AT THE CROSSROADS
As potential indications emerge, limits and questions also surface

by Howard Larkin

Over the past decade, corneal collagen crosslinking has revolutionised treatment of progressive keratoconus. Over the next decade, crosslinking could play a significant role treating refractory infectious keratitis and non-infectious melting syndromes, and stabilising corneas after laser refractive surgery to prevent regression and possibly ectasia.

Moreover, new crosslinking techniques could make corneal crosslinking more patient-friendly. UV-A irradiation times will almost certainly shorten while targeted radiation could customise crosslinking to strengthen the cornea overall by increasing the volume of polymerised tissue, or to promote specific corneal remodelling. (Kanellopoulos AJ, Asimellis G. Clin Ophthalmol. 2013;7:329-35.)

It may even be possible to eliminate the need to remove the epithelium – along with the pain, extended recovery time, corneal haze and infection risk that go with it – for at least some indications. Eventually, sunlight might replace UV-A irradiation and aldehyde sugars might replace riboflavin – or intrastromal glucose administration could supplant photosensitizers and UV-A altogether.

“We know how to shorten irradiation time and we can reverse corneal melting. Other techniques are in development in the field,” said Theo Seiler MD, PhD. (Kanellopoulos AJ. Clin Ophthalmol. 2012;6:97-101.)

Now at the University of Zurich, Switzerland, where he also heads the Institute for Refractive and Ophthalmic Surgery, Prof Seiler and colleagues developed corneal crosslinking at the University of Dresden in the late 1990s and early 2000s. He spoke on the future of corneal crosslinking in his keynote lecture at the 2012 cornea subspecialty day of the American Academy of Ophthalmology.

But while crosslinking appears safe and has entered the mainstream nearly everywhere but the US, where FDA trials are still under way, questions remain.

Why does crosslinking fail to prevent progression of corneal steepening in about three per cent of patients? (Koller et al. J Cataract Refract Surg 2009; 35: 1358-62.) What parameters contribute to continuing corneal flattening, which often stabilises at two years, but can go on for four or more years? And what are the long-term effects of greatly accelerating stiffening that naturally occurs with ageing?

As experience with corneal crosslinking grows and its technology develops, both its potential and its limits are getting clearer.

Avoiding PK Crosslinking was developed to avoid penetrating keratoplasty (PK). Before crosslinking, keratoconus treatment was limited to spectacles followed by rigid contacts as the disease progressed. As many as one in five patients ultimately required PK to rescue vision. (Lass JH et al. Ophthalmology. 1996; 97(4): 433-445.)

With mean graft survival estimated at 17 years for primary PK, and less for repeat procedures, the lifetime burden is high for the typically young keratoconus patient. (Borkerie VM et al. Ophthalmology 2012; 119(2): 249-255.) In theory, switching to deep anterior lamellar keratoplasty (DALK) for patients with intact endothelium could extend graft survival to a mean 49 years. But this has not yet been demonstrated in practice, and DALK refractive outcomes are no better than PK. (Reinhart WJ et al. Ophthalmology. 2011; 118(1): 209-18.)

By contrast, a meta-analysis of randomised contralateral eye-controlled corneal crosslinking studies found that it not only halts keratoconus progression in nearly all adult patients at 12 months’ follow up, it actually leads to regression of 1.0 D or more in central cornea steepness in nearly half. (Gore RM et al. Eye 2012 Dec 21 epub ahead of print.) In addition, a continuous reduction in irregular astigmatism is typically seen, leading to a mean improvement in spectacle corrected vision of about two Snellen lines, generally stabilising about two years after surgery in adults. (Caporossi A et al. Am J Ophthalmol. 2010; 149(4): 585-93.)

Crosslinking also appears to be safer. One IROC study of 117 eyes in 99 patients found just 2.9 per cent losing two or more Snellen lines, with sterile infiltrates seen in 7.6 per cent and central stromal scars in 2.8 per cent. Preoperative maximum keratometry of 58.0 D or more was a significant risk factor for failure, and a preoperative corrected vision of 20/25 or better increased risk for complications. (Koller JCRS 2009.)

Other common complications include pain, photosensitivity, corneal haze and microbial keratitis, due to removal of the protective epithelium. Less common is endothelial damage due to thin corneas. Persistent corneal oedema and non-infectious corneal melt after crosslinking also have been reported.

The impact of age The IROC study also found patient age higher than 35 years significantly increased complication risk, illustrating one way in which age influences crosslinking outcomes. It concluded that restricting patient age to younger than 35 could reduce complication rates to one per cent.

Patients 18 years and younger also respond differently to corneal crosslinking, in part because keratoconus is much more aggressive in children, said Paolo Vinciguerra MD, Instituto Clinico
Crosslinking and LASIK
As with keratoconus, the inexorable progression of istrogen keratocasis led Prof Seiler to turn to crosslinking in 2003. In 46 cases in which he waited, all progressed within six months by more than 1.0 D, so he decided not to wait.

One of Prof Seiler’s first post-LASIK crosslinking patients was a 32-year-old female who developed a steep central island 18 months after LASIK. Prior to crosslinking, the treated eye had not progressed, but the fellow eye had. As of late 2012, the crosslinked eye still had not progressed. If anything, there was a little bit of improvement in topography, he noted.

To date, progression stopped at 12 months’ follow up in all 24 keratocasis patients, 22 post-LASIK and two post-photorerefractive keratectomy (PRK) patients, that Prof Seiler has treated. None lost more than two lines of corrected vision while eight gained more than two lines uncorrected. Progression was halted in all of these 12 patients reaching five years follow up: eight had Kmax reduced more than 2.0 D, five saw more than two lines improvement in uncorrected visual acuity and none saw deterioration of best corrected vision.

One patient suffered endothelial damage in a case where a thin cornea did not swell enough when treated with hypotonic riboflavin solution. “We did the crosslinking anyway because the alternative would have been DALK. The patient took the risk but the cornea never cleared,” Prof Seiler said.

After stabilising keratocasis with crosslinking, Prof Seiler has seen good results with stromal ring segments for visual rehabilitation. One patient improved from 0.3, or about 20/70, to 0.8, or 20/25, one month after one stromal ring was inserted. Rigid contacts are another option, as is surface ablation since there is no flap to affect biomechanical stability.

“We could risk it, but many patients don’t want to do laser anymore,” he noted.

However, A John Kanellopoulos MD, of Athens, Greece, and NYU Medical School, New York City, US, has developed a procedure combining topo-guided partial PRK and crosslinking for keratoconus and keratectasia. Known as the Athens Protocol, a WaveLight excimer laser guided by Placido- and/or Pentacam-derived topographic imaging removes no more than 40 to 50 microns to regularise corneal topography. Mitomycin-C is applied and higher-fluence crosslinking is performed to stabilise the result. (Kanellopoulos AJ. The Athens Protocol: PRK and CXL. Chapter 8 in: Present, Past and Future. Slack Incorporated 2012)

Previously he crosslinked first and PRK later (Kanellopoulos AJ, Binder PS. Cornea. 2007 Aug;26(7):891-5), but found better results doing the procedures together. Mean corrected visual acuity was logMAR 0.11+/-. 0.16 for combined procedures compared with 0.16 +/- 0.22 for sequential (p<0.001), and lower mean K decreased 3.5 D v 2.75 D, respectively (p<0.005).


It appears that doing both at the same time is synergistic, he noted. He emphasised, though, that this is not a refractive procedure. Corrected vision improves due to reductions in corneal asymmetry, but there is no attempt to correct refractive error. The procedure also appears safe. In a series of 412 cases treated with the Athens Protocol, less than one per cent progressed, and less than five per cent had delayed epithelial healing and/or stromal scarring. (Kanellopoulos AJ, Cho M.: Complications with the Use of Collagen Cross-Linking. Chapter 10 in: Complications in Ocular Surgery. Slack Incorporated 2012.)

Dr Kanellopoulos has had success preventing the shift to instability in the system, including cataract surgery, he commented. LASIK weakens the cornea by one-quarter to one-third, while a -6.6 LASIK changes corneal power 0.15 dioptre in corneal power every year.


Dr Kanellopoulos crosslinked these patients by applying a 0.1 per cent riboflavin solution to the exposed stroma after ablation, and irrigated through the repositioned flap with a higher fluence lamp delivering 10 mW/cm² for 10 minutes through the repositioned LASIK flap using the Avedro, KXL device. He has since increased UVA fluence to 30mW/cm² exposed for 80 seconds.

Using the same approach, Dr Kanellopoulos has had success preventing the long-term progression usually seen in hyperopic LASIK treatment. Two years after surgery, 34 eyes treated with very high-fluence crosslinking, 30mW/cm² for 80 seconds, after LASIK saw a mean change in keratometry of less than 1.0 D in treated eyes compared with nearly 3.0 D with standard hyperopic LASIK in contralateral control eyes. (Kanellopoulos AJ, Kohn J. J Refract Surg. 2012 Nov;28(11 Suppl):S837-40.)

“For hyperopes, crosslinking is the key to keep long-term results stable,” Dr Kanellopoulos said. The impact of LASIK instability may be even more evident when measured by long-term keratometrical stability than visual acuity, he added.

John Marshall PhD, of Kings College, London, UK, suggested that accelerated crosslinking should be used with all laser refractive procedures both to stabilise refractions and prevent ectasia.

Any surgical intervention will increase the shift to instability in the system, including cataract surgery, he commented. LASIK weakens the cornea by one-quarter to one-third, while a -6.6 LASIK changes corneal power 0.15 dioptre in corneal power every year.

Dr Marshall’s research suggests applying riboflavin beneath the flap enables crosslinking above and below the flap interface, stabilising the entire cornea.

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Easing the pain

Though preferable to transplantation, standard crosslinking is still inconvenient and painful. It takes 30 minutes of riboflavin soak, reapplied frequently, followed by 30 minutes of UV-A at 3 mW/cm². Moreover, removing the epithelium is painful, taking several weeks to recover. Techniques are in the works that may address these problems.

Cutting irradiation time by increasing source power may be the easiest.

“Tissue absorbs energy, not power, and energy is power times time. We can play around with the power-time complex to deliver the same amount of energy to the cornea in less time,” Dr Marshall explained.

Dr Marshall’s research suggests that three minutes at 30 mW/cm² is safe.

“It’s clear we can shorten the irradiation with the optimum power somewhere between 10 and 20 or 25 mW,” said Prof Seiler, who established the current standard through hundreds of experiments.

Irradiation devices with higher fluence and customisable depth may also make possible custom crosslinking that strategically reinforces corneal tissue rather than stiffening the maximum volume, which may stress surrounding tissues including the limbus, trabecular meshwork, iris and crystalline lens, Dr Kanellopoulos said.

“In the near future, we may be crosslinking ‘beams’ or ‘patterns’ of cornea tissue and not entire areas.”

Shortening riboflavin imbibition time is more difficult, Dr Seiler said. It takes 30 minutes for riboflavin to soak in 330 microns, which is essential to maximise the volume of crosslinked tissue he noted. A 15 minute soak cuts the depth to about 200 microns.

Do not perform crosslinking on a LASIK patient until such time as we can determine the risks and benefits.

Perry Binder MD

Leaving the epithelium intact has advantages, including quicker healing and reduced infection risk, but is problematic. Riboflavin is a large molecule, and it will not penetrate the tight junctions of the epithelium unless they are loosened, with agents. Nonetheless, trans-epithelial crosslinking using permeability enhancing agents, such as trometamol, EDTA and BAK, has been successful. (Filipello et al. J Cataract Refract Surg. 2012 Feb; 38(2): 283-91.)

Iontophoresis, which uses a negative charge on the eye to pull in riboflavin, may also help. (Vinciguerra P ESCRS 2012.)

However, trans-epithelial crosslinking is limited to about 100 to 140 microns (Caporossi A Eur J Ophthalmal 2012), and the stiffening effect is about one-fifth that of the standard technique. (Wollensak G et al. J Cataract Refract Surg 2009; 35: 540-546.) Worse, at two years, it has shown signs of regression. (Caporossi A EVER 2012.)

Prof Seiler finds these defects fatal, but is confident that trans-epithelial methods will be devised that will equal the soaking performance of the epithelium-off standard.

Still, current transepithelial crosslinking may be effective in very thin corneas, children and uncooperative patients, noted Leopoldo Spadea MD, associate clinical professor of ophthalmology, chief of corneal and refractive surgery – Eye Clinic, S. Salvatore Hospital, University of L’Aquila, Italy. But will it succeed? “Only time will tell.”

Future uses and techniques

In addition to biomechanical effects, crosslinking also has cytotoxic and biochemical properties, Prof Seiler said. These may lead to new applications.

Crosslinking kills keratocytes down to about 300 microns. It also kills everything else, making it a remarkably effective broad-spectrum anti-microbial, Prof Seiler said. In one study, infectious corneal melting was halted in five eyes, avoiding emergency keratoplasty. (Iseli HP et al. J Refract Surg. 2011 Mar;27(3):195-201.)

Biochemically, crosslinking makes the cornea more resistant to enzyme erosion, Prof Seiler said. As a result, it can also heal inherited non-infectious corneal melting.

In a normal cornea, the extracellular matrix is synthesised by keratocytes at the same rate it is eaten up by enzymes in the tear film. But in melting syndromes, synthesis doesn’t keep up, Prof Seiler explained. Crosslinking inhibits enzyme catalysis, bringing it back into balance with synthesis. He has used it to arrest and reverse a case of Terrien’s marginal degeneration, for which no other treatment is known.

Eventually, the entire riboflavin-UVA process could be replaced, Prof Seiler said. Sunlight is as effective as a UVA lamp. And glucose will stiffen the cornea just as well as riboflavin. “The problem is it takes about 20 days.” “It could be that you take eye drops a few times a day and sit in the sun and you get well,” Prof Seiler said.

A president of EuCornea, Jose I. Guell MD, Barcelona, Spain, often hears from surgeons confused by conflicting case reports about new corneal collagen crosslinking applications. He believes international clinical societies can help by standardising patient evaluation practices and ensuring that studies are properly designed and adequately powered.

“When a new instrument is in the hands of doctors we have a tendency to invent new indications and this is often very useful. But only properly designed, long-term studies will clearly show to everyone if something is working. Big societies must organise or co-organise these studies,” Dr Guell said.

Standardising evaluation and outcomes reporting will also help address concerns that available topographic and tomographic instruments are less accurate detecting changes in highly aberrated eyes.

“If we all use the same techniques to examine patients, then we can compare the results,” Dr Guell said.

A panel assembled by EuCornea, the Cornea Society and the South American Cornea Society are developing standards for new strategies for managing keratoconus, Dr Guell said. Long-term controlled studies of higher power UV devices and new riboflavin solutions to shorten treatment time, and iontophoresis to promote trans-epithelial procedures, are under way.

“In the next one or two years we will have enough data from good controlled studies to know if they are effective and safe.”

Confirming new crosslinking indications, including reducing chronic corneal oedema and stabilising corneal grafts in keratoconic or trauma patients, will take longer.

“From an economical point of view, these other indications are not very significant. Crosslinking appears very useful to control infectious keratitis, but we all need a significant number of cases and follow-up before we can understand it not as a single case, but to demonstrate this is a useful technique. This will take three or four years depending on the level of interest,” Dr Guell said.

Contact: Jose I. Guell guell@oma.es

LEOPOLDO SPADEA

Cover Story

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