

Corneal collagen cross-linking – fact not fiction

Sean Henahan reports on the EuroTimes Roundtable discussion at the 12th ESCRS Winter Refractive Surgery Meeting in Barcelona



José Guell



Francois Malecaze



Joseph Colin



Theo Seiler

Scepticism concerning corneal collagen cross-linking is now giving way to enthusiasm as clinical studies begin to yield meaningful results, particularly in the treatment of progressive keratoconus. *EuroTimes* convened a roundtable to discuss the current state of this procedure at the 12th ESCRS Winter Refractive meeting. Jose Guell MD moderated the discussion, which included Francois Malecaze MD, Joseph Colin MD, and Theo Seiler MD, PhD.

Dr Guell: Cross-linking is most often associated with treatment of keratoconus, but keratoconus covers a wide spectrum of disease. What patients should be considered the best candidates for collagen cross-linking?

Dr Malecaze: The answer is very clear. We don't know yet what is the real effect of this treatment, so from my point of view we should only be treating progressive keratoconus. Some people treat keratoconus with the idea of preventing progression, but based on what we know today we should limit ourselves to treating patients with progressive disease to try to stop that progression.

Dr Colin: I agree 100 per cent. Today we have the responsibility to determine what the optimal indication for cross-linking is. This is a new technology with very short follow-up, and with no control group. There is no prospective study that has demonstrated results in patients with similar degrees of keratoconus at similar stages, showing a difference between cross-linking and placebo. Based on our current knowledge, our indications are progressive keratoconus with two options. If the patient has progressive keratoconus and is contact lens tolerant we go ahead with cross-linking. If the patient is contact lens intolerant, we prefer to first perform an Intacs implantation, then we wait three to six months until we obtain the maximum effect of the Intacs, and then we perform cross-linking. We do not recommend this treatment in very advanced cases of keratoconus where there is progression, and if there are opacities in the centre. If the cornea is thinner than less than 350 microns there is no chance to improve the visual quality of these patients.

Dr Seiler: The best-case scenario is a 15-year-old, with history of progressive keratoconus, where you have personally demonstrated the progression with the Pentacam over a period of months. We would treat that patient with cross-linking right away. The worst-case scenario is the 55-year-old guy who has had stable pellucid margin degeneration, with some inferior scarring. That patient does not need cross-linking; he needs rings for optical rehabilitation, maybe keratoplasty.

In our clinic we have another clear urgent indication: whenever we cannot stop melting of the cornea, whether it is infectious or non-infectious, we use cross-linking with good success in those cases. A publication regarding this indication is under way. We also consider cross-linking for cases of progression of keratectasia where there is no good alternative, for example in keratectasia after LASIK as soon as it is diagnosed.

Dr Guell: Intacs have been mentioned as a complement to cross-linking. We also hear of other combinations, such as using RK, PRK. What do you think of those?

Dr Malecaze: Dr Seiler has proposed a wonderful idea, to perform cross-linking to stiffen the cornea and then perform a topography-guided photoablation. I think this would be a good strategy. My question is, are we sure we have really stiffened the cornea enough to perform a topography-guided PRK? For example, in our series one patient continues to progress even after cross-linking treatment.

Dr Seiler: The first step, in my mind, is to cure the disease, that is, to stop the progression. The next step is optical rehabilitation. I am not sure whether this can be done the other way around or at the same time. We are doing a study at the moment using the Ziemer laser, inserting rings at the same time that we do cross-linking. Then at one and three months we can shift the rings according to the changed axis, to optimise the optics of that cornea. I do have my doubts regarding PRK after cross-linking. On the one hand we are stiffening the cornea making it stronger, creating an armour around the cornea, and then we begin removing it

with PRK. There is a concern about progression and we need more information to establish criteria regarding remaining thickness, etc. Meanwhile we have two case reports of cross-linking and PRK where keratoconus progression did occur. We should also remember that many patients can wear contact lenses again after the procedure. Our opticians tell us it is so much easier to fit new contact lenses after cross-linking.

Dr Colin: One of the most difficult situations for us today is a patient who comes in for refractive surgery but topographically is a keratoconus suspect. The cone is not progressive, but we are not happy to suggest a laser treatment. Would you recommend cross-linking in a patient with no progression?

Dr Seiler: It might well be that in a couple of years this would be an accepted procedure, but right now we are in the evaluation phase. We don't really know the indications or the contraindications of CXL; we do not know which kind of keratectasia responds the best to this treatment.

Dr Malecaze: We will be able to answer these questions when we have a clinical test that can measure the viscoelasticity of the cornea.

Dr Seiler: Even if we have appropriate measurements, and Dr Cynthia Roberts is investigating the viscoelasticity of the cornea in cross-linked and non-cross-linked eyes, we still have to wait until we have the long-term data. We will need at least 10 years of follow-up. Remember with all the refractive procedures in the cornea we are stuck with the same problem. The cowboys come in and say wow that is something new we can do this - and do it in a large number. We saw it with RK; we saw it with LASIK for 20 D. But then two, five, 10 years later, the cornea responded in an unexpected way.

Dr Guell: We are hearing of variations on the cross-linking technique, with some trying to move corneal abrasion, for example. What should be the protocol for the ideal, randomised clinical trial?

Dr Malecaze: Dr Seiler's group has shown that if you want the riboflavin to penetrate the cornea you need to take off the epithelium. He has also provided the experimental data supporting the safety of his protocol for the endothelium, the lens and the retina,

Dr Colin: We follow the protocol suggested by Dr Seiler. We remove the epithelium, and then we use a soft suction system, put the drops inside the tube, and have a perfect constant 8.0mm flow, with no riboflavin going to the limbal cells. This creates a

kind of riboflavin bell. After 20 minutes it is perfect, we dry the cornea, and remove the tube.

Dr Seiler: Let's separate fact and fiction. The fact is that we remove the epithelium and it works, the fiction is that we leave the epithelium but break the barrier function, it should work also. Dr Pinelli presented a paper where he showed some effect with this approach. We will attempt to reproduce this in Zurich. If it turns out to work, then we will have to start the whole evaluation again. The crucial thing is that if you have the right concentration of riboflavin in the cornea, then you can create sufficient radicals to produce cross-linking. There are several ways to do this; you don't have to follow our strict protocol, as long as you can guarantee that the cornea is yellow and saturated with riboflavin.

Dr Malecaze: It is important to note that you must examine the patient under the slit-lamp. You cannot do this treatment without looking. It is important to be able to see the penetration of riboflavin inside the cornea and the anterior chamber.

Dr Guell: What are the risks if the riboflavin has not penetrated the cornea?

Dr Seiler: There is a risk of less effect. It is just cheating the patient, who believes that the doctor did the best job to preserve his cornea. Some have expressed concern about potential toxicity to the lens and retina, but we selected our protocol with that in mind. With UV 360nm, the lens and retina and endothelium are not at risk. There is good data to support this. We would have loved to use a higher wavelength, and the equipment exists to do this, but then if something was not right, there could be harm to the endothelium and the retina.

Dr Guell: What is the suggested postoperative regimen? Do you use steroids?

Dr Malecaze: The rationale for using steroids is to reduce inflammation and associated haze. We know that steroids have no negative effect on the cross-linking itself.

Dr Colin: Steroids do not inhibit the cross-linking effect, but after the procedure there are some changes in the cornea, with regeneration of keratocytes etc. Maybe corticosteroids have some influence on what happens to the cornea in the days following cross-linking. We have no data comparing steroids and no steroids in the immediate post-op period.

Dr Seiler: I agree steroids have no influence on the cross-linking itself, but the healing takes months or even years before the keratocytes have repopulated that area. Of course the patient would like to have a non-inflamed, calm eye, which is why I am giving mild steroids just to make the eye white as soon as possible.

Dr Malecaze: In my first 20 patients I had the wrong idea that steroids might interfere with the cross-linking, so I didn't give them to my patients. In those patients we saw haze immediately post-op, but this was gone after two months.

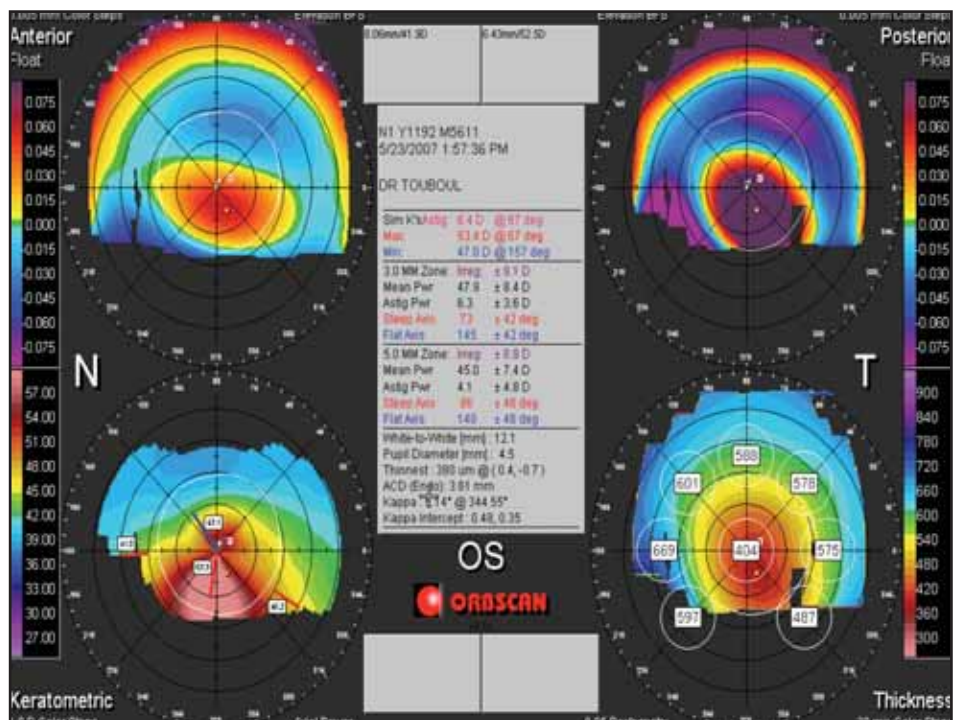
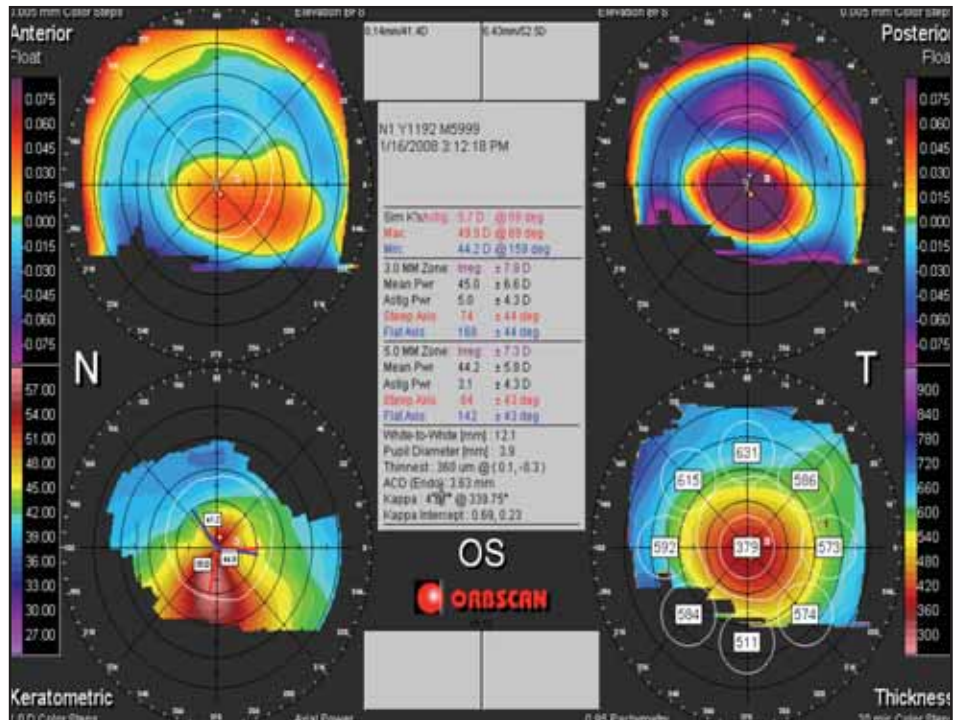
Dr Guell: What other post-op complications should we be aware of?

Dr Seiler: We have seen one case of stromal scarring and several late epithelial healing cases. We know this from other corneal procedures such as PRK. The stromal scar disappeared within six months.

Dr Colin: We have seen one case of infectious keratitis that was referred to us. We have seen five cases of delayed epithelial healing. This is not too surprising. These are not normal corneas. We are used to having quick re-epithelialisation following PRK in normal young corneas. With keratoconus

we have steep corneas, and breaks in Bowman's membrane. We see some haze during the first weeks in about one third of patients, which disappears.

Dr Seiler: This points again to the potential value of preserving the epithelium. It might be possible to take only 10 or 20 microns of epithelium via PTK, which might allow sufficient penetration of riboflavin. We are doing these studies, and I would be very happy if other groups also joined this research.

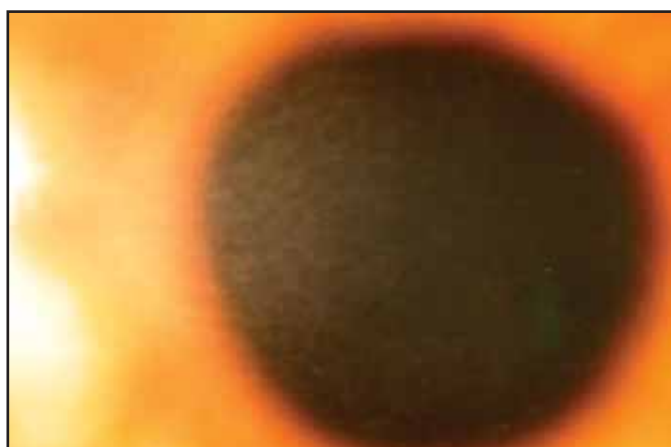
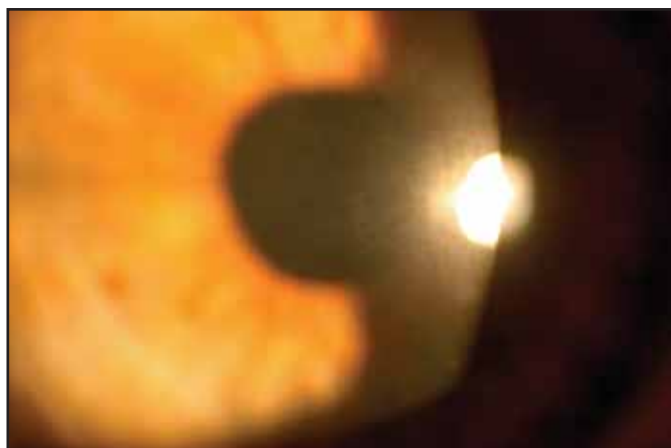


Dr Guell: What is the learning curve for this surgery and who should be performing it?

Dr Colin: The surgical procedure is relatively simple to learn. The most important thing is that surgeon should have global training in the field of cornea, particularly in the management of keratoconus, and ectasia. You cannot do this procedure if you don't understand corneal responses, corneal healing, and the normal evolution of keratoconus. Cross-linking is a new attractive treatment option for patients with progressive keratoconus, but it is only one of several corneoplastic procedures. The patient will be best served by a practice that can offer all options, not just cross-linking. I do have some concern that the reputation of the procedure could decrease because of bad surgery.

Dr Seiler: In terms of learning the procedures and handling the complications, I advocate seeing an experienced corneal surgeon to learn everything about keratectasia. It would probably not make sense for a retina surgeon who shifted over to refractive surgery to start doing cross-linking; it would not be beneficial to patients. We are currently in the phase of establishing the criteria for treatment and we are seeking the help of doctors who will communicate not only their successes but also complications. I encourage doctors to share their problems so we can all learn.

malecaze.fr@chu-toulouse.fr
info@iroc.ch
joseph.colin@chu-bordeaux.fr
guell@imo.es



Clinical results at one month

Early clinical results

Corneal collagen cross-linking involves abrading the central cornea, applying riboflavin, and then applying UV light at 370nm for 20 to 30 minutes, which enhances corneal biomechanical stability by creating new chemical bonds between collagen molecules.

Clinical data on cross-linking have been somewhat sparse. Aldo Caporossi MD, Siena, Italy, recently presented a three-year follow-up of a series of 44 keratoconic eyes treated with cross-linking. The eyes showed marked improvements in visual acuity along with an apparent stabilisation of disease. Mean uncorrected visual acuity improved from 20/100 preoperatively to 20/40 at two years' postoperatively. Mean best-corrected visual acuity improved from 20/33 preoperatively to 20/25 postoperatively. Five eyes developed transient haze, which disappeared after three weeks.