Assessing three treatment modalities for keratoconus

Intacs, crosslinking or a combination. Which is best?

BY YARON S. RABINOWITZ, MD

Intracorneal ring segments and collagen crosslinking (CXL) have gained increasing interest in management of patients with keratoconus, in large part due to the pioneering work of Joseph Colin in France and Theo Seilers’ group in Dresden, Germany.1-3 In the United States, the only approved intracorneal ring segments are Intacs (Addition Technology, Lombard, Ill.).

They can be implanted under a Humanitarian Device Exemption in patients who are over 21, have stable disease, a clear visual axis and who have become contact lens intolerant. CXL has been used for over a decade in Europe, but is not FDA approved in the United States.3

It is, however, being increasingly studied under a variety of protocols either institutional review board (IRB)-monitored or off-label by numerous physicians throughout the United States.

DETERMINING THE BEST TREATMENT

At the Cornea Eye Institute in Beverly Hills, California, we are studying CXL under an investigational device exemption from the FDA monitored by Western IRB. (ClinicalTrials.gov Identifier: NCT01081561). The main goal of our study is to determine long term which is best, CXL alone or a combination of CXL and Intacs.

We can enroll up to 800 patients and to date have treated 350 patients with keratoconus and or ectasia, with annual follow-up for all patients for five years. We have been performing Intacs for 10 years and CXL for the past four years. The clinical dilemma that often arises is which treatment modalities to pursue for an individual keratoconus patient: Intacs alone, CXL alone or combination therapy? While we don’t have an exact answer because of the variable response to treatment by individual keratoconus patients, this article attempts to answer these questions based on our experience up to now.

INTACS ALONE

Best candidates

Fifteen years ago, Joseph Colin, MD, was the first to demonstrate that by inserting intracorneal rings into patients with moderately advanced keratoconus you could flatten the cornea and improve uncorrected and best-corrected vision. Results were best in patients who were contact lens intolerant, but also in selected patients tolerant of contact lenses, or in some cases who were making the transition from a rigid contact lens to a soft contact lens.1,2

In our own experience, this procedure has about a 70% success rate in carefully selected candidates. Ideal candidates are contact lens intolerant, have a maximum keratometry that does not exceed 58 D, have no central or para central scarring, are at least 450 µm thick at the 7-mm optical zone and are nonprogressive in nature. Most importantly, these patients should have realistic expectations in that they will still need glasses or contact lenses for optimal distance.
acuity.

**The procedure**

We use a femtosecond laser to create the channels and typically create the channels at 400 µm in depth. We have found the use of the laser creates a more reliable channel at intended depth, with better visual outcomes and less chance of erosion due to the rings being placed too superficially, which tends to occur more commonly using the mechanical technique.\(^4\)\(^,\)\(^5\) We use OCT, videokeratography and manifest refraction to plan our surgery and typically try to transect the thinnest part of the cornea with the ring, to restore physiological normality.

In cases where the cone is located inferiorly or inferotemporally and the refractive error includes a large amount of regular astigmatism in addition to the irregular astigmatism found in keratoconus, we will use a single inferior ring only. If the refractive error is mild and we think we can improve vision by improving the spherical equivalent, we will use two asymmetric rings: typically a 0.45 µm ring inferiorly and a 0.25 µm ring superiorly. Visual improvement is usually due to reduction in the irregular astigmatism as demonstrated by a decrease in higher-order aberrations on wavefront analysis.\(^4\)\(^,\)\(^5\)

**Success with Intacs**

As previously mentioned, the key to success with this procedure is adequate patient selection. Patients with realistic expectations will be happy, while those who expect to see well without contact lenses or glasses may be disappointed. Improving adequate patient selection comes with experience and requires the practice of the “art as well as the science of medicine.”

We do not insert Intacs to stop progression. The main indications for Intacs are to flatten the cornea, improve contact lens tolerance and possibly improve uncorrected and best-corrected acuity. On average you can flatten the cornea by 2 D and gain approximately two lines of improvement in vision in 60% to 70% of eyes.

The results are variable, though, with some patients getting up to five lines of improvement while others may see no improvement at all.

**CXL ONLY**

**Choosing the epi-off protocol**

The excellent laboratory work in preclinical experiments and the large body of literature supporting its efficacy and safety convinced me that the “epi-off” Dresden CXL protocol was a good treatment modality to pursue for patients with progressive keratoconus.\(^6\)\(^-\)\(^10\)

We do not perform “epi-on” CXL currently for several reasons. Among them:

1. Work in the lab by Wollensak shows that even if the riboflavin penetrates the stroma, the stiffening effect is only 28% of that achieved with epi-off CXL.\(^11\)

2. For a crosslinking reaction to take place, oxygen is necessary; leaving the epithelium on is a barrier to oxygen so the crosslinking reaction may not be as efficacious.

3. The epithelium is a barrier to UV light, so to get the same effect as epi-off, the energy has to be significantly increased. No studies exist which show that higher energy levels with the epithelium on is safe for the eye. Our inclusion criteria for crosslinking treatments in our study are essentially conservative and based on Seiler’s original recommendations.\(^6\) They are:

- Progression of myopia and or cylinder by refractions of at least 1 D, confirmed by topographic evidence of keratoconus in the year preceding treatment or topographic evidence of progression of Max K or Average K over the prior year
- Pachymetry as measured by corneal OCT of no less than 400 µm
- Central K readings not exceeding 58 D
• No central or para central corneal scarring.

We have been following the Dresden protocol for the vast majority of our patients: this involves removing the epithelium, soaking the cornea with riboflavin for 30 minutes and then treating with UV light for another 30 minutes with 3mW/cm². We have modified the epithelial removal of the Dresden protocol somewhat in that we remove the epithelium with the phototherapeutic keratectomy (PTK) mode using the VISX laser (Abbott Medical Optics, Abbott Park, Ill.) as recently described by Kymionis from Greece and Bruce Jackson’s group in Canada. This smooths out the irregularity at the apex of the cornea, resulting in better visual acuity compared to pure mechanical removal as described in the Dresden protocol.

**Variations of epi-off CXL**

In instances where the cornea is less than 400 µm but not less than 350 µm, we have started using hypotonic solution, or have just swelled the cornea with regular balanced salt solution for 15 minutes prior to treatment. We are doing this only in a highly select few cases and our outcomes have been reasonable. In cases where we believe the outcomes will be less than optimal — even after crosslinking — because of severe central corneal irregularity, we have recommended penetrating keratoplasty or deep anterior lamellar keratoplasty to spare the need for an additional procedure prior to proceeding to a transplant.

Recently, based on safety studies in two published papers, we have switched our protocol to the accelerated method: soaking the eye with riboflavin for 20 minutes and providing high-intensity irradiation for 10 minutes with 9 mW/cm² of UV-A irradiation. This protocol appears to have the same effect as the standard protocol and cuts the treatment time down to 30 minutes, which is a major advantage.

**Success with crosslinking**

Our data shows that epi-off crosslinking works in that it halts progression and in many instances produces regression of the disease. Approximately 60% to 70% of patients get improvement of at least one line or more of vision at one year and we have seen up to four lines improvement by three years in some instances (**Figure 1**).

![Figure 1](http://www.ophthalmologymanagement.com/printarticle.aspx?articleID=111673)
We do not offer CXL to improve vision, but only to halt progression. CXL is our treatment of choice for patients with progressive disease only. If patient vision improves, we consider it a bonus.

**COMBINED INTACS AND CXL**

**When is it appropriate?**

I am often confronted with the question as to whom to do intracorneal rings on only, whom to do cross-linking on only, and which patients should have both crosslinking and intracorneal rings done at a single session. In general, I tell patients that collagen crosslinking is done to halt progression and intracorneal rings are performed to improve vision or contact lens tolerance.

If the patient wants improved vision early on and wants to stop the progression of the disease, I will do both intracorneal rings and crosslinking during the same session if their refractive error is myopic. I do not encourage this and tell patients that having the procedure three months apart is the more conservative approach. Preliminary analysis of our data suggests that in terms of long-term outcomes it does not matter whether they are done simultaneously or three months apart.

If I do the two procedures simultaneously, I will first make the tunnels with the femtosecond laser, then remove the epithelium with PTK. I follow this with collagen crosslinking and then insert the rings after completing the crosslinking. Using this technique, the results have been very good (Figure 2). Whether to do crosslinking only, intracorneal rings only, or both simultaneously is dependent on the clinical situation and a judgment based on individual surgeon experience at the time of the procedure.

![Figure 2: A 26-year-old male with progressive keratoconus right eye, wanted to stop progression and improve vision. Preoperative acuity was 20/150 and Max K in this eye was 47.33. Three months later, uncorrected acuity in this eye improved to 20/25 and Max K was reduced to 44.38. This patient underwent combined Intacs and Collagen Cross linking in the same session. COURTESY: YARON S. RABINOWITZ, MD](image)

**Considering a combination**

To improve vision and flatten the cornea to improve contact lens tolerance, Intacs works well. To halt the progression of keratoconus — epi-off crosslinking works very well. If patients are myopic and want both early improved vision and to halt the progression of keratoconus, they might consider a combination of Intacs and CXL. OM
REFERENCES


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Disclosure: He is the principal investigator on a study on collagen cross linking and Intacs for Keratoconus.