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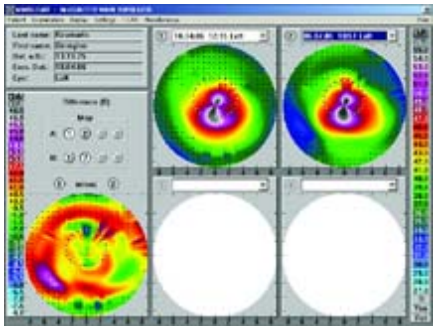
REFRACTIVE SURGERY

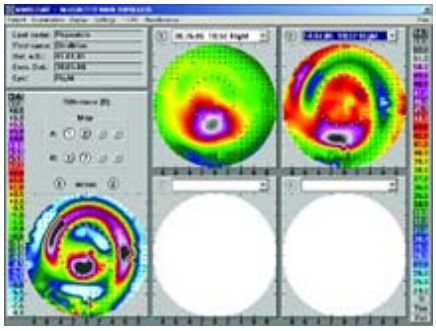
Keratoconus: at a crossroads

by Maxine Lipner EyeWorld Senior Contributing Editor

Collagen crosslinking holds appeal for keratoconus and other diseases



This patient's pre- and post-collagen crosslinking topography shows stabilization and some reduction in cone steepness
Source: A. John Kanellopoulos, M.D.



This patient had collagen crosslinking performed in the past for keratoconus; after undergoing subsequent PRK, the cornea is stable three years out and improved BSCVA from 20/50 to 20/25; here we see the patient's pre- and post-topo-guided PRK treatment topographies and the topography showing the difference
Source: A. John Kanellopoulos, M.D.

When it comes to keratoconus treatment, practitioners have had very limited options—relying on use of rigid gas permeable contact lenses or, more recently on use of Intacs (Addition Technology, Des Plaines, Ill.) to help alleviate visual problems. One new potential treatment in the wings for this is use of collagen cross-linking. This holds promise not only but for keratoconus for other diseases as well, in addition to having refractive potential, according R. Doyle Stulting, M.D., Ph.D., professor of ophthalmology, Emory University, Atlanta.

To date, however, most of the work that has been done with the collagen crosslinking technique has been in conjunction with keratoconus. A. John Kanellopoulos, M.D., associate clinical professor of ophthalmology, New York University, New York, and director of laser vision, GR Institute, Athens, Greece, has been using the technique in keratoconus patients for years. The innovative method received the CE Mark in all 25 European countries as of December 2006, according to Dr. Kanellopoulos.

Building new bridges

"The way the treatment works is that it forces the collagen fibers in the cornea to develop new binding bridges between them," he said. "It is as if we had a ladder and we're adding more steps to that ladder. It makes the edges of the ladder become much more stable in between them."

There are actually two elements involved in the cross-linking process: ultra violet radiation and vitamin B2, also known as riboflavin. The riboflavin absorbs a lot of ultraviolet A radiation. "There is a property of riboflavin that makes it absorb a lot of bad radiation and create free radicals," Dr. Kanellopoulos said. "This chemical reaction of creating free radicals forces the collagen fibers that are innocent bystanders in this chemical reaction to crosslink."

Dr. Kanellopoulos recently used the technique in the case of a patient with bilateral, progressive keratoconus. Topical 0.1% riboflavin drops

were placed on the de-epithelialized cornea of the left eye. Then UVA radiation at a dose of 3 millowatts per square centimeter was shone on the corneal surface for 30 minutes. In the case study, which was recently published in a recent issue of Cornea, there was a significant clinical improvement. After the crosslinking procedure the patient's uncorrected vision improved from 20/100 to 20/80, and best corrected visual acuity improved from 20/50 to 20/40.

At the one-year mark topographically-guided PRK was also performed in one eye with a refractive error of –3.50 D. Eighteen months after the PRK procedure the patient's UCVA was at 20/20 and BSCVA was 20/15. In the meantime, the keratoconus continued to progress in the patient's untreated right eye.

Since this initial case, investigators have discontinued the one-year waiting period between the collagen crosslinking and PRK procedures and now perform the limited refractive procedure first. "Our current protocol is to do the crosslinking and the PRK in the same sitting," Dr. Kanellopoulos said. "Our percentage of needing to refine the corneal correction is under 10%." This underscores the advantages of performing both procedures at once. "Not only did the patient have to have only one procedure, but we feel that there are inherent advantages to this routine," Dr. Kanellopoulos said.

In particular, performing both procedures at the same time with the PRK first tends to minimize any potential scarring from the PRK. The cross-linking procedure causes a transient loss of stromal keratocytes. If the practitioner waits in between procedures these keratocytes replenish and are fresh during the PRK and can cause more scarring. "If you do your limited-topoguided PRK procedure first, the UVA that follows reduces the keratocytes that would induce the scarring mechanism," Dr. Kanellopoulos said. "This was the main reason why we switched the sequence of our technique. We found that doing the topoguided treatment first compliments the cross-linking in regard to avoiding corneal haze."

While a keratoconus patient can have an excellent visual result with the addition of the PRK procedure, completely removing a high level of refraction is not the goal here, according to Dr. Kanellopoulos. "We have placed a 'ceiling' to the amount of tissue that we're removing to 40 microns," he said. "This is a very limited PRK and its goal is not to correct the refractive error, but to normalize the cornea."

Refinements

New possibilities with the collagen cross-linking are also beginning to emerge. Dr. Kanellopoulos' team has been experimenting with cutting down the amount of time needed for the procedure. "We are experimenting with delivering the same energy in a shorter amount of time by doubling the fluence," he said. "We have found that 7 milliwatts per square centimeter may be a reasonable means of cutting down on the treatment time, going from 30 minutes to 15 with the same total irradiance of about 5.5 joules."

Another refinement, investigators are also looking into is sidestepping the scraping of the corneal epithelium. "We're looking into the possibility of using the IntraLase (Advanced Medical Optics, Santa Ana, Calif.) in some eyes to create a corneal pocket at 100 microns depth and instilling a one-time, one-dose amount of 0.1% riboflavin in that pocket," Dr. Kanellopoulos said. "We would then cross-link the cornea selectively, 60 microns above the pocket and 200 microns below without having to remove the corneal epithelium."

Dr. Stulting sees the technique as holding great promise. Currently he views the two-pronged cross-linking PRK approach, or using cross-linking together with insertion of Intacs, as useful for those with more advanced

disease. “For those who have advanced disease stiffening the cornea and freezing it into position so that it doesn’t change will prevent progression but it won’t improve the current status very much,” he said. For those with early disease cross-linking alone may be enough. “Looking down the road to the future, the standard of care will probably become one of detecting keratoconus very early on and cross-linking those people so that they never develop the disease and therefore do not need these treatments,” he said.

New spins

In addition to using collagen cross-linking for keratoconus, there are several interesting new uses on the horizon. Dr. Stulting sees the technique as having potential applicability for stabilizing the cornea for non-surgical refractive techniques such as orthokeratology. “Now orthokeratology is a technique in which hard contact lenses are worn overnight to temporarily change the corneal shape,” he said. “The possibility arises that you could use the orthokeratology lenses at night and then the next day when your corneal is a normal shape you could cross-link it and it would stay that way.”

A second possibility is that collagen cross-linking could be used as a treatment for corneal melting disorders such as those affecting patients with rheumatoid arthritis. “A side effect of the cross-linking is to increase the resistance to enzymatic degradation,” Dr. Stulting said. “So, all those diseases in which there is enzymatic degradation might be benefited by cross-linking.”

Yet another potential use is for the treatment of difficult infectious diseases such as deep fungal infections or acanthamoeba. “When you expose a riboflavin soaked cornea to UV light it liberates reactive oxygen species,” Dr. Stulting said. “Those may be sufficiently toxic to microorganisms that it might be useful as a treatment.”

***Editors’ note**: Dr. Stulting has financial interests with Priavision (Menlo Park, Calif.). Dr. Kanellopoulos has financial interests with Wavelight (Erlangen, Germany) and Priavision.*

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