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CORNEA

## The latest in crosslinking

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by **Enette Ngoei EyeWorld Contributing Editor**

*EyeWorld looks at the hottest areas in corneal crosslinking for the treatment of keratoconus*

**C**onsidering that keratoconus is the second most common reason why patients undergo corneal transplantation in the U.S., Eric D. Donnenfeld, M.D., co-chairman of Cornea, Nassau University Medical Center, East Meadow, N.Y., said it is unfortunate that U.S. patients are the only ones in the world who cannot have corneal crosslinking treatment done in an FDA-approved way.

It's been well established through worldwide experience that corneal crosslinking is an essential step in preventing keratoconus progression, said John Kanellopoulos, M.D., associate clinical professor of ophthalmology, New York University, New York, and director of laser vision, GR Institute, Athens, Greece.

So while the ophthalmology community in the U.S. continues to await FDA approval, surgeons elsewhere are advancing their research beyond the standard technique used to treat keratoconus patients.

### **Beyond epi-off**

One area of interest in crosslinking is whether there can be deviation from the standard epithelium-off method to an epithelium-on method.

The risks of the epithelium-off method are small, Dr. Donnenfeld said. It has the risk of epithelial defect, similar to PRK, which has been done for 20 years in the U.S., and many studies have shown that the risk of infection is about 1 in 500, and the risk of vision loss is about 1 in 5,000, he said.

So why the need for deviation?

"I think the major reason why physicians are doing epithelium-on is for comfort; it's certainly more comfortable and people can go back to work more quickly," he said.

Epithelium-on crosslinking has gained some support in the U.S., although there's no scientific data to support epithelium-on crosslinking as being equal and certainly not superior to epithelium-off crosslinking, Dr. Donnenfeld said.

"As a matter of fact, at the European Crosslinking Congress, which [recently] took place, there was a lot of data presented that suggested that epithelium-on crosslinking is not as effective as epithelium-off," he said.

Transepithelial crosslinking is an area that's been studied by many groups and shows some promise, Dr. Kanellopoulos said. "We're not certain we'll get the same amount of crosslinking when we work transepithelially because some of the UV light is blocked by the epithelium. We're not sure how much riboflavin is penetrating within the cornea."

"I think it's a great idea to do epithelium-on crosslinking in theory, but I think it's irresponsible to do epithelium-on crosslinking routinely on all patients until there's data that shows that it's as good as epithelium-off, especially in a number of more aggressive crosslinking patients," Dr. Donnenfeld said.

Some surgeons, including Dr. Donnenfeld, are doing partial epithelium-off crosslinking where they make little holes in the epithelium using devices, which gets better levels of riboflavin into the stroma, he said.

There are others who are making pockets in the corneal stroma with lamellar incisions and using these incisions to apply crosslinking at a deeper level in the cornea, which is in a very early stage and is a controversial area as well, he added.

## Other areas of interest

Researchers are also exploring whether or not crosslinking can be done at the same time as excimer laser photoablation.

In Europe, surgeons are routinely doing topographic ablations on patients with keratoconus and crosslinking them at the same time, Dr. Donnenfeld said.

Probably one of the most interesting areas in crosslinking today is the use of increased energy and reducing the time period of crosslinking, Dr. Donnenfeld said.

"We introduced the concept of higher fluence crosslinking 5 years ago with the thought of delivering the same energy to the cornea and reducing the potential toxicity of longer duration of UV exposure to the cornea," Dr. Kanellopoulos said.

Traditionally, crosslinking is done with 3 mW/cm<sup>2</sup>, and now there are crosslinking units that have up to 30 mW for the same area. It's suggested that the crosslinking time can be reduced to 3-5 minutes, so there can be a much shorter time period, Dr. Donnenfeld explained.

"We have seen it clinically work identical to shorter fluence crosslinking, and now we're seeing a lot of groups [creating] commercial products that embrace this technique," Dr. Kanellopoulos said.

According to him, Avedro (Waltham, Mass.) has a device that goes up to 45 mW fluence. IROC (Zurich, Switzerland), which is the think tank of the original crosslinking procedure, has just introduced a device that goes up to 10 mW, and Peschke Meditrade GmbH (Zurich, Switzerland) introduced a device that goes up to 18 mW, Dr. Kanellopoulos said.

Dr. Donnenfeld cautioned that there's not a lot of data comparing these to the traditional crosslinking done with a 3 mW unit.

## Rethinking crosslinking itself

Researchers are also revisiting the process of crosslinking.

"We always thought that crosslinking was a photochemical type 2 reaction run by the oxygen singlets produced by the sensitized riboflavin," Dr. Kanellopoulos said.

However, experiments done by Avedro recently in cadaver corneas that mimicked the standard technique showed that the oxygen is depleted in the cornea within almost a minute through the procedure and is replenished about 20 minutes into the procedure, he said.

"That raises a big question mark. What runs the reaction between minute 1 and minute 20? There's speculation that there's another type of photochemical reaction, which is run not by the oxygen singlets, but riboflavin itself

becomes a triplet and it may directly crosslink the cornea," Dr. Kanellopoulos explained.

If the actual vehicle of crosslinking is riboflavin, it changes the whole protocol of how the drops are applied, how the cornea is exposed, and so on, he said.

"There's a lot of work that needs to be done in this direction. I personally am starting to tap into the knowledge of photosensitizing by riboflavin, which is very vast in sterilization of blood products. There are commercially available techniques of inserting riboflavin within plasma, for example, which is high risk for transfusion, and then sensitizing with UV

### EyeWorld factoid

**Keratoconus is the most common corneal dystrophy in the U.S., affecting one in every 2,000 Americans. It is more prevalent in teenagers and adults in their 20s**

Source: National Eye Institute, National Institutes of Health

light in order to create sterilization of that packet," Dr. Kanellopoulos said.

**Editors' note:** *Dr. Donnenfeld has no financial interests related to this article. Dr. Kanellopoulos has financial interests with Avedro.*

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