Corneal collagen crosslinking continues to be a hot topic in ophthalmology. Still seeking FDA approval in the U.S., the technology has been showing promising results in an Avedro trial. Clinical trials are currently in process of seeking FDA approval and other institutional Institutional Review Board (IRB) trials, leading more and more physicians to get on board with it. In addition, combinations of crosslinking with other therapies have begun to emerge, and studies are being undertaken to determine results of crosslinking with Intacs (Addition Technology, Des Plaines, Ill.), LASIK, and other procedures.

**Current state of crosslinking**

"There are a plethora of studies that are ongoing right now, and it's very easy to get into these studies so that patients do have access to crosslinking," Dr. Donnenfeld said. Discussions on crosslinking bring up two main issues, he said, which are how the riboflavin is applied and the duration of the treatment. Advancements in studies progress have allowed for shorter treatment times and less invasive transepithelial procedures.

"Crosslinking worldwide has been around for several years now, and I think that the consensus in the field is that it's something that is a very useful technique for the treatment of keratoconus and corneal ectasia with the goal of decreasing the progression of these disease processes, as well as in some cases actually improving vision," Dr. Hersh said.

"In the U.S. there was an original multicenter clinical trial, and that currently is sponsored by Avedro," he said. This trial has been completed and is currently going through the FDA submission process. "This is occurring now," Dr. Hersh said. "The hope is that this would ultimately lead to FDA approval."

The results in safety and efficacy were "quite encouraging," Dr. Hersh said. Though the actual clinical trial was completed and analyzed, it took some time for the study to be approved, which the study group is expecting.

"Dr. Muller, the only one that has a trial at this point, is trying to produce some data from this trial, to submit the new protocol to the FDA in order to seek approval for another trial," Dr. Hersh said. "But even after this trial to the FDA for approval, it will be another months or so to do this.

Though the results so far come as encouraging, Dr. Hersh said, "and the next year, Dr. Hersh said, "and the protocol of crosslinking in the U.S. are much more effective."

Dr. Hersh completed an accelerated crosslinking protocol currently being used with patients. In addition, he indicated that he is a multi-center study looking at the effects of crosslinking on CXL USA.

Dr. Rubin said that with CXL USA because the results have been encouraging, they have begun to have a "take off" in the U.S. "With the advice from physician associations, some physicians have used CXL. This is called it CXL USA."

Dr. Rubin said he has grown from a few cases to more than a dozen. "We have over a dozen cases now, and the number of patients is growing," he said. "It's also convenient for us to get a clear result and amend protocols accordingly."
was completed several years ago, it took some time to complete the data analysis and move on to the submission stage. Dr. Hersh indicated that the study is proceeding at an expected pace.

Dr. Muller said that Avadro is the only company so far in the U.S. that has a trial that is expected to produce some sort of approval for crosslinking. He said Avadro expects to submit the data from its clinical trial to the FDA sometime in September. “With a little luck, we hope that approval will be within six months of that submission,” he said.

Though this approval could come as early as the first quarter of next year, Dr. Muller noted that it would just be for the first generation protocol of crosslinking, based on data from some years ago. Current crosslinking being done around the world and trials starting now in the U.S. are much more advanced than that, he said. Newer protocols include shorter procedure time with more effective parameters.

Dr. Hersh said Avadro has completed another clinical trial of accelerated crosslinking, which is currently conducting follow-up with patients. In addition to Avadro’s work, he indicated that there is a multicenter study with transepithelial crosslinking being conducted by CXUFA.

Dr. Rubinfeld is currently working with CXUFA, which he started because the rest of the world seemed to have access to a treatment for keratoconus that was not available in the U.S. “With a group of excellent physicians and a lot of regulatory advice from professionals and some significant personal funds, I started a physician-sponsored, IRB-approved, clinical study in the U.S., and we call it CXUFA,” he said.

Dr. Rubinfeld said CXUFA has grown from a single site to now more than a dozen with about 38 investigators across the U.S. “We have over many years, with several protocols, been treating quite a number of patients with superb results,” he said. IRB studies are convenient for being able to modify and amend protocols based on rapid analysis of data, Dr. Rubinfeld said.

Other forms of crosslinking and possible combination therapies

Dr. Hersh said his center is involved in a multicenter clinical trial with crosslinking being used as an adjunct to LASIK. Earlier this year, Dr. Hersh visited Colombia to examine the technique for performing crosslinking as an adjunct to LASIK. The clinical trial will be starting in the U.S. looking at hyperopic LASIK using adjunctive crosslinking, he said. Patients with between 2.0 D and 6.0 D of hyperopia will be eligible.

Dr. Hersh said there have been other studies to look at crosslinking with a combination of procedures. “We have been undertaking a trial looking at combination therapies, in particular crosslinking with Intacs,” he said.

With crosslinking, the main goal is to strengthen the weak cornea and prevent progression, while Intacs aims to flatten the cone and make the cornea more symmetric. Since the two procedures have different clinical objectives, it would seem that these therapies would work well together. Dr. Hersh said there were two goals of this experiment: to look at safety and efficacy using these procedures adjunctively and to see if the timing for the procedures was important. He said it had to be determined clinically whether it was better to do the two concurrently or if they should be spaced.

Although the study is still ongoing, early analysis suggested that the use of these two treatments is effective, and there does not seem to be a major difference between concurrent and sequential surgery, Dr. Hersh said.

“If I think crosslinking and Intacs is a great solution,” Dr. Donnenfeld said. The crosslinking will help prevent progression of the disease, while Intacs helps to improve vision.

In addition to crosslinking with LASIK and crosslinking with Intacs, worldwide there have been experiments with the combination of crosslinking and topography-guided PRK. Although this is not available in the U.S., there have been encouraging results elsewhere, Dr. Hersh said. “I think that crosslinking as an adjunctive procedure to a number of [procedures] is something that we’re going to be seeing more and more of,” he said.

Dr. Rubinfeld discussed a combination therapy with crosslinking that CXUFA developed a protocol for about 15 months ago. “We have been combining conductive keratoplasty (C.K., Refractive, Bloomington, Minn.) with crosslinking,” he said. Both are epo-on procedures and both are relatively non-invasive. “We have found incredibly rapid visual recovery and marked improvement in the regularity of the corneas.” So far, results are stable and there are impressive data over a 12-month period. “One of the problems with CK in the past is that the results didn’t necessarily last as long,” he said. However, by combining the treatments with crosslinking, this has helped to “lock in” the effect of CK, and Dr. Rubinfeld said it “has been astonishingly effective in quite a number of eyes.”

The future of crosslinking

Dr. Hersh said he believes that international clinical trials and U.S. multicenter clinical trials show good evidence that it’s a “safe and effective procedure.” He said that moving forward, some of the important issues to examine are efficacy of transepithelial crosslinking, the safety and efficacy of accelerated crosslinking with higher power, and the use of accelerated crosslinking as an adjunct to LASIK.

“We know crosslinking works,” Dr. Rubinfeld said. There have been dozens of well-performed studies, he said. “I can’t express in words how gratifying it is to stop patients from losing their vision to irregular astigmatism in keratoconus and post-LASIK excimer.” Dr. Rubinfeld said he is pleased with the data from CXUFA, which demonstrates good efficacy and reduced risk with the epi-on procedure as compared with making a large epithelial defect in the epi-off procedure.

“There’s no question that corneal strengthening is one of the major advances in the last several years and will be one of the key advances in ophthalmology for at least a decade as we move toward refractive indications and other indications,” he said.

Dr. Donnenfeld said his hope is that keratoconus becomes a disease similar to polio in that it ceases to exist because there is a therapy that can stop the disease. “The morbidity and quality of life associated with keratoconus mandates that we as compassionate ophthalmologists implement this treatment, which can change literally thousands of lives on an annual basis,” he said.

“Ophthalmology in the U.S. is certainly ready for crosslinking to be approved, and I believe we have the data to support that,” Dr. Muller said. “Hopefully the FDA will agree with us.”

Editors’ note: Dr. Hersh has financial interests with Avadro. Dr. Rubinfeld has financial interests with CXUFA and CXLO. Dr. Donnenfeld has no financial interests related to this article. Dr. Muller has financial interests with Avadro.

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The Vibex is now exposed to the UV illumination through the flap and its intact epithelium to facilitate cross-linking.

In this video, Avadro describes Lasik Xtra, corneal crosslinking during a LASIK procedure to preserve corneal biomechanical integrity.

Source: Avadro