



REGULATORY/LEGISLATIVE

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FDA backs launch of collagen cross-linking clinical trials

International data have shown that the procedure helps halt the progression of various corneal diseases.

by Erin Boyle

The U.S. Food and Drug Administration has approved three clinical trials to evaluate the safety and efficacy of corneal collagen cross-linking for the treatment of progressive keratoconus and corneal ectasia.

The randomized, controlled clinical trials are expected to be launched by the end of January, R. Doyle Stulting, MD, PhD, said in a telephone interview with *Ocular Surgery News*.

International data indicate that corneal collagen cross-linking, which is not yet approved for use in the United States, enhances biomechanical stability of the cornea, halting the progression of keratoconus and post-LASIK ectasia, according to Dr. Stulting.

The trials are designed to assess the safety and efficacy of cross-linking with riboflavin and ultraviolet-A (UVA) light.

The riboflavin and UVA light are administered using carefully selected parameters that limit cross-linking to the initial 300 μm of the cornea, avoiding damage to the corneal endothelium, the crystalline lens and the retina.

"Current management of progressive keratoconus consists of spectacles, rigid gas permeable contact lenses and corneal transplantation — but these are temporary treatment modalities that do not alter the underlying process of corneal steepening, thinning and scarring, with eventual loss of uncorrected and best corrected vision," Dr. Stulting said. "Keratoconus is the underlying disease responsible for about 15% of the corneal transplants performed in the United States. Thus, corneal collagen cross-linking is a potential cure for a vision-threatening, life-altering, economically significant disease for which we currently have no cure."

The procedure has other potential applications, such as stabilization of autoimmune corneal melts, improvement of visual function in eyes with pseudophakic corneal edema and treatment of drug-resistant microbial keratitis.

Identical clinical trials

The first trial will take place at Emory University in Atlanta under a physician-sponsored Investigational New Drug application process. The other two trials, which are sponsored by the Switzerland-based company Peschke Meditrade, will be conducted at six to 10 facilities in the United States. Dr. Stulting will serve as principal investigator for the first trial and medical monitor for the other trials.

Other investigators who will participate in the clinical trials are: Perry S. Binder, MS, MD, from San Diego; Eric D. Donnenfeld, MD, and Marguerite B. McDonald, MD, both from Long Island, N.Y.; Francis W. Price Jr., MD, from Indianapolis; Roger F. Steinert, MD, from Irvine, Calif.; Stephen Trokel, MD, from New York, and Peter Hersh, MD, from Teaneck, N.J.





**R. Doyle
Stulting**

Each trial is expected to include 160 patients with keratoconus and 160 patients with corneal ectasia. Half of the patients will be treated with corneal collagen cross-linking and half will serve as controls. The trials will utilize identical procedures and protocols.

The change in corneal curvature in the treated group will be compared with that in the untreated group. Uncorrected and best corrected vision will be secondary outcome measures.

Corneal collagen cross-linking is performed by removing the corneal epithelium and applying topical riboflavin drops.

After saturation of the cornea with riboflavin is verified by slit lamp examination, the eye is exposed to ultraviolet light at carefully determined intensity for 30 minutes. The UV light interacts with the riboflavin, producing reactive oxygen species that create chemical bonds between and within corneal collagen fibrils, making them stiffer, Dr. Stulting explained.

“The technique strengthens the cornea — an effect that is obvious in the laboratory,” he said. “It has applications in diseases that involve progressive corneal stretching due to biomechanical instability. These include the naturally occurring diseases, keratoconus and pellucid marginal degeneration, as well as one that is aided, created or stimulated by refractive surgery, which we call ectasia after LASIK.”

European findings cited

Dr. Stulting cited European studies by Theo Seiler, MD, PhD, and others on the use of corneal collagen cross-linking to improve corneal biomechanical stability and either stop or deter the progression of post-LASIK ectasia.

“International data indicate that cross-linking not only prevents the progression of keratoconus but also causes a slight regression of the disease with a flattening of the keratometry, improvement in uncorrected visual acuity and improvement in best spectacle- corrected visual acuity,” he said. “Even more exciting is the long-term follow up of these patients who seem to maintain the effect of treatment indefinitely.”

Cross-linking, which has been studied since 1998 at the University of Dresden, has few side effects. Typically, corneal haze is seen in the anterior stroma after treatment, but it resolves with time. It is thought that the haze is related to keratocyte apoptosis and regeneration after cross-linking.

A randomized clinical trial is under way in Australia, Dr. Stulting said.

“All of the studies conducted outside the United States have produced similar data. In fact, the benefit of treatment in the Australian clinical trial is so striking that consideration may be given to discontinuation of the study in the near future for ethical reasons,” he said.

“We have not been able to perform this procedure legally in the United States because it is not approved by the FDA. Being able to begin our cross-linking trials finally enables us to provide our patients in the United States with the same level of care that our international colleagues can provide.”

For more information:

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Reference:

- Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol.* 2003;135:620-627.
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