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Prospective Randomized Trial of Corneal Cross-linking Riboflavin Dosing Frequencies for Treatment of Keratoconus and Corneal Ectasia

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Purpose: To investigate whether the riboflavin dosing frequency affects corneal cross-linking efficacy or safety, given that isotonic riboflavin solution is viscous and each installation coats the corneal surface with a film that absorbs some of the incident ultraviolet A light.

Design: Prospective, randomized, single-center equivalence trial.

Participants: Patients with progressive keratoconus or ectasia after refractive surgery (n = 510).

Methods: One eye per patient was prospectively randomized to 2-minute or 5-minute riboflavin dosing intervals with standard corneal cross-linking (epithelial removal and 30-minute irradiation with 3 mW/cm^2 ultraviolet A light). Block randomization resulted in comparable representation of keratoconus and ectasia after refractive surgery in the 2 treatment arms. Treatment equivalence was assessed using the 2 one-sided test. Fellow eyes (n = 207) were treated with 5-minute dosing and considered in the safety analysis.

Main Outcome Measures: The primary hypothesis was equivalent change in the topography-derived maximum keratometry value from baseline to 6 months with 2-minute vs. 5-minute dosing. A ±0.75-diopter margin of equivalence for the treatment difference between dosing regimens was considered clinically relevant. Adverse events and changes from baseline to 6 months in corrected distance visual acuity (CDVA), uncorrected distance visual acuity, and minimum corneal thickness were assessed.

Results: The mean reduction in maximum keratometry from baseline was equivalent with 2-minute and 5-minute riboflavin dosing intervals at 6 months (0.97 and 0.76 diopters, respectively; 90% confidence interval for treatment difference, −0.23 to 0.66; per-protocol population). With both dosing intervals, the mean improvement in CDVA was 0.07 logarithm of the minimum angle of resolution or 3.5 letters at 6 months. Of the 635 study and fellow eyes examined at 6 months, 134 (21%) gained and 32 (5%) lost 2 or more lines of CDVA. Three eyes (0.4%) developed sterile infiltrates, 1 (0.1%) had delayed epithelial healing with dendrites, and 3 (0.4%) had recurrent epithelial defects. Three eyes (0.4%) were re-treated.

Conclusions: The 2 riboflavin dosing regimens produced equivalent reduction in the maximum keratometry value, with a favorable safety profile. *Ophthalmology 2017;■:1−7 © 2017 by the American Academy of Ophthalmology*

Corneal cross-linking (CXL) has become a widely accepted treatment used to strengthen the cornea and thereby halt the progression of keratoconus or corneal ectasia after refractive surgery. An expert panel listed CXL as a first-line surgical treatment for keratoconus and ectatic diseases in a 2015 global consensus document,[1] and CXL was approved by the United States Food and Drug Administration for treatment of keratoconus and ectasia after refractive surgery in 2016.

CXL involves instillation of riboflavin eye drops to saturate the cornea and irradiation with ultraviolet-A (UVA) light to trigger chemical bonding within the cornea.[2] During irradiation, each application of the standard viscous riboflavin solution coats the corneal surface with a film that absorbs some of the incident UVA light.[3,4] Laboratory studies show that the surface film thickness varies with the riboflavin formulation and dosing time, and that the film significantly impacts UVA absorption.[3,4] Thus we hypothesized that the riboflavin dosing frequency might affect CXL efficacy. Controlled clinical studies investigating this are lacking.

The standard Dresden CXL protocol involves removal of the corneal epithelium, soaking the corneal stroma with riboflavin, and irradiating the cornea with UVA light (3 mW/cm^2) for 30 minutes. Riboflavin dosing regimens of 2 to 5 minutes have been used: riboflavin/dextran ophthalmic solution was applied every 4 to 5 minutes during irradiation at the Dresden clinic,[5] every 3 minutes in an Australian randomized clinical trial,[6] and every 2 minutes in the United States multicenter clinical trials.[7,8] The purpose of this study was to investigate whether 2- and 5-minute riboflavin dosing frequencies produced equivalent outcomes.

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Methods

This prospective, randomized trial assessed the equivalence of 2 riboflavin dosing regimens for CXL. Institutional review board approval was obtained. The study adhered to the tenets of the Declaration of Helsinki and complied with the United States Health Insurance Portability and Accountability Act. Study subjects completed a written informed consent process. The study was submitted to the Food and Drug Administration as a physician-sponsored investigational new drug application and was registered at ClinicalTrials.gov (NCT01143389).

Inclusion/Exclusion Criteria

The inclusion/exclusion criteria were similar to those used in U.S. clinical trials that established CXL efficacy with a 2-minute riboflavin dosing interval.[7,8] The inclusion criteria were male or female gender, any race or ethnicity, age 10 years or older, and diagnosis of keratoconus or ectasia after previous refractive surgery as documented by topography or tomography. Subjects who were over 25 years old and were diagnosed with keratoconus had to have exhibited progression within 36 months before randomization, as defined by 1 or more of the following: (1) $\geq$1.00 diopter (D) increase in the steepest keratometry value (or sim K); (2) $\geq$1.00 D increase in cylinder on subjective manifest refraction; (3) $\geq$0.50 D increase in myopia on subjective manifest refraction; (4) documented decrease in visual acuity associated with worsening irregular astigmatism and topographic features of ectasia.

Subjects diagnosed with keratoconus had to have axial topography consistent with keratoconus, central or paracentral elevation on corneal tomography, and presence of 1 or more characteristic slit-lamp findings (e.g., Fleisher ring, Vogt striae, or apical thinning). Contact lens wearers were required to remove contact lenses before the screening refraction for the following lengths of time: 3 days for soft lenses, 1 week for soft extended-wear lenses, 2 weeks for soft toric lenses, and 3 weeks for rigid gas-permeable lenses.

Exclusion criteria were as follows: previous ocular conditions that could predispose to complications such as herpes simplex, herpes zoster keratitis, recurrent erosion syndrome, corneal melt, corneal dystrophy, etc.; clinically significant scarring in the proposed treatment zone; insufficient corneal stromal thickness by tomography mapping; a history of chemical injury or delayed epithelial healing; a known sensitivity to treatment medications; a current condition that in the treating physician's opinion would interfere with or prolong epithelial healing; pregnancy or lactation during the course of the study.

Study Examination Schedule and Procedures

Subjects underwent a screening examination up to 60 days before treatment and were examined 1 day, 1 week, 3 months, and 6 months after treatment at Price Vision Group, Indianapolis, IN, between June 2010 and June 2017. The screening examination included medical, ocular, and medication histories, as well as uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) measured with a Snellen chart; manifest refraction; corneal tomography (Pentacam; Oculus, Inc., Arlington, WA); corneal topography (Tomey, Nagoya, Japan); intraocular pressure by Goldmann applanation; slit-lamp examination of the cornea, anterior chamber, and lens; and dilated fundus examination. The 1-day posttreatment visit included slit-lamp examination and UDVA. The 1-week visit included slit-lamp examination, intraocular pressure, and UDVA. The 3- and 6-month examinations were performed by masked examiners and included slit-lamp examination, intraocular pressure, UDVA, CDVA, manifest refraction, corneal tomography, and topography.

Randomization

Randomization occurred immediately before treatment. Subjects were classified as having keratoconus or ectasia after refractive surgery. In addition, those with keratoconus were graded as mild, moderate, or severe as described by the Collaborative Longitudinal Evaluation of Keratoconus Study Group.[9] Block randomization was used to ensure representation of each classification in both treatment groups. A web-based random number generator was used to develop the randomization schedule for each classification. The randomization schedules were stored in sealed, consecutively numbered envelopes. A study coordinator opened the next envelope from the appropriate classification group to reveal the riboflavin dosing frequency (2-minute or 5-minute interval during irradiation) right before the investigator initiated the treatment.

Fellow Eyes

Patients could have both eyes treated if the investigator thought the treatment could be beneficial in both eyes. Only the first treated eye per patient was considered for the efficacy analysis, whereas all treated eyes were included in the safety analysis. Fellow eyes could be treated on the same or a different day as the randomized eye, as decided by the patient and the investigator. Fellow eyes were not randomized and received riboflavin at a 5-minute dosing interval during irradiation.

Cross-linking Treatment

The CXL treatment matched that used in the U.S. clinical trials except that we randomized participants to different riboflavin dosing regimens.[7,8] Before use, the UV-X illumination system (IROC, Zurich, Switzerland) was assembled and tested according to the manufacturer's instructions. The UVA irradiance dose is the product of the irradiance intensity and the exposure time. The intensity is a fixed parameter of the device and is checked to ensure it is within the appropriate range before use.

The subject reclined on a surgical table and the treatment eye and periocular areas were prepared with betadine. Topical anesthesia was applied and a speculum was placed to hold the eyelids open. The surgeon removed the central 9 mm of corneal epithelium. Additional local anesthetics were applied as needed throughout the treatment.

The lid speculum was removed and 0.1% riboflavin/20% dextran ophthalmic solution was instilled topically every 2 minutes for 30 minutes. Corneal thickness was measured by ultrasonic pachymetry and if the minimum thickness was at least 375 μm the irradiation was started. Otherwise, balanced salt solution was instilled to swell the cornea to at least 375 μm. In 9 cases, a riboflavin-soaked non-UVA-blocking plano soft contact lens (approximately 100 μm thick; Biofinity; CooperVision, Scottsville, NY) was applied to increase the minimum thickness to at least 375 μm before initiating irradiation.[10]

The lid speculum was reinserted and the eye was aligned under the UV-X light with the treatment plane at a working distance that was 50 mm from the UV-X beam aperture, which was set to 9.5 mm. The eye was irradiated for 30 minutes, during which time instillation of riboflavin continued (1 drop every 2 minutes or every 5 minutes, depending on the randomization). At the end of 30 minutes, the ultraviolet light source automatically switched to the off position. The operator also tracked the irradiation time independently. A drop of antibiotic and a bandage contact lens were placed in the eye, which was examined at a slit lamp. Patients were prescribed a topical antibiotic to be used 4 times daily until epithelialization was complete, topical prednisolone acetate 1% to be used 4 times daily for 2 weeks, and preservative-free artificial