Effect of the Direct Application of Riboflavin and UVA on the Visian Implantable Collamer Lens

Farhad Hafezi, MD, PhD; Francois Majo, MD, PhD; Alaa M. El Danasoury, MD, FRCS

ABSTRACT

PURPOSE: To report the effect of corneal collagen cross-linking (CXL) with riboflavin and ultraviolet A (UVA) on the optical and material characteristics of a posterior chamber phakic intraocular lens (Visian ICL, STAAR Surgical).

METHODS: Optical and material characteristics were assessed in vitro, analyzing potential changes in riboflavin staining, dioptric power, transmission characteristics, and surface structure. A total of 9 lenses were analyzed: 3 lenses were irradiated with 0.23 mW/cm^2, the maximal intensity that may be encountered during actual surgery; 3 lenses were irradiated with 2.3 mW/cm^2, 10 times the maximal intensity encountered during surgery; and 3 lenses served as controls.

RESULTS: Following CXL with UVA and riboflavin, no changes were observed in the parameters tested; in particular, dioptric power and transmission characteristics were similar before and after CXL.

CONCLUSIONS: Cross-linking with UVA and riboflavin does not affect the optical and material characteristics of the Visian ICL after irradiation with the maximal UVA energy levels that may be encountered during surgery. Even when the UVA irradiation dose was increased by a factor of 10, no changes were observed. [*J Refract Surg*. 2010;26(10):762-765.]

doi:10.3928/1081597X-20100415-01

The Visian Implantable Collamer Lens (ICL; STAAR Surgical, Monrovia, California) is a phakic intraocular lens that is used for the treatment of moderate to high myopia, hyperopia, and astigmatism. The lens is made from Collamer, a biocompatible material based on hydrophilic porcine collagen, and is designed to be implanted into the posterior chamber behind the iris.[1] The ICL is commercially available in three models—myopic, hyperopic, and toric. The powers range up to −23.00 diopters (D) for myopia, up to +21.50 D for hyperopia, and 6.00 D of astigmatism. The ICL and toric ICL have several potential advantages: preservation of corneal shape and hence the quality of vision, possibility of correcting high amounts of myopia without compromising corneal biomechanics, and removability and exchangeability. The Visian ICL is approved by the US Food and Drug Administration to treat up to −15.00 D of myopia with <2.50 D of astigmatism. In patients with myopia who may not be suitable candidates for excimer laser procedures for various reasons, it may represent a safe and effective alternative.[2-5] In patients suffering from keratoconus, ICL and toric ICL alone or in combination with Intacs implantation (Addition Technology, Des Plaines, Illinois) is used to correct the spherical component of ametropia (myopia and hyperopia).[6-10]

Corneal collagen cross-linking (CXL) with ultraviolet A (UVA) and riboflavin is a technique that modifies the biomechanical and biochemical properties of the human cornea. Its main indications are progressive primary (keratoconus, pellucid marginal degeneration) and secondary (iatrogenic) keratectasia,[11-13] although the method has also been successfully applied for a variety of other indications, eg, visual fluctuations in Fuchs dystrophy and corneal melting.[14,15] Using the standard CXL treatment protocol, the anterior eye is irradiated with a set dose (3 mW/cm^2 or 5.4 kJ at the surface level) of UVA light at a wavelength of 365 nm.

The ICL has also been indicated for use in patients with stable keratoconus and patients with keratoconus whose corneal condition has been stabilized by CXL or intracorneal ring segments.[8,9] On the other hand, the clinical course of keratoconus often is unpredictable, where periods of progression may alternate with periods during which the ectatic process appears to have arrested.[8,9] Many patients who received an ICL or toric ICL during a period of keratoconus stability may need CXL at a later stage should the ectasia progress.

Because UVA and high-energy, short-wavelength visible light may induce damage of intraocular structures,[16-18] we tested whether the UVA irradiation used during CXL might have unwanted effects on the optical and material characteristics of the Visian ICL.

MATERIALS AND METHODS

Experimental Setup and Determination of the Maximal Irradiation Dose

In a first step, the irradiation dose that should be

From Institute for Refractive and Ophthalmic Surgery (IROC), Zurich, Switzerland (Hafezi); Hôpital Ophtalmique Jules Gonin, Lausanne, Switzerland (Majo); and Refractive Surgery and Cornea Unit, Magrabi Eye & Ear Hospital, Jeddah, Saudi Arabia (El Danasoury).

Drs Hafezi and El Danasoury are consultants for STAAR Surgical, Nidau, Switzerland. Dr Majo has no financial interest in the materials presented herein.

The authors thank Dr Eberhard Spoerl, University Eye Clinic Dresden, for calculation of the irradiance intensity at the level of the STAAR Visian Implantable Collamer Lens.

Correspondence: Farhad Hafezi, MD, PhD, Institute for Refractive and Ophthalmic Surgery (IROC), Stockerstrasse 37, 8002 Zurich, Switzerland. Tel: 41 43 488 3800; Fax: 41 43 488 3809; E-mail: farhad@hafezi.ch

Received: October 16, 2009; Accepted: April 8, 2010

Posted online: May 3, 2010

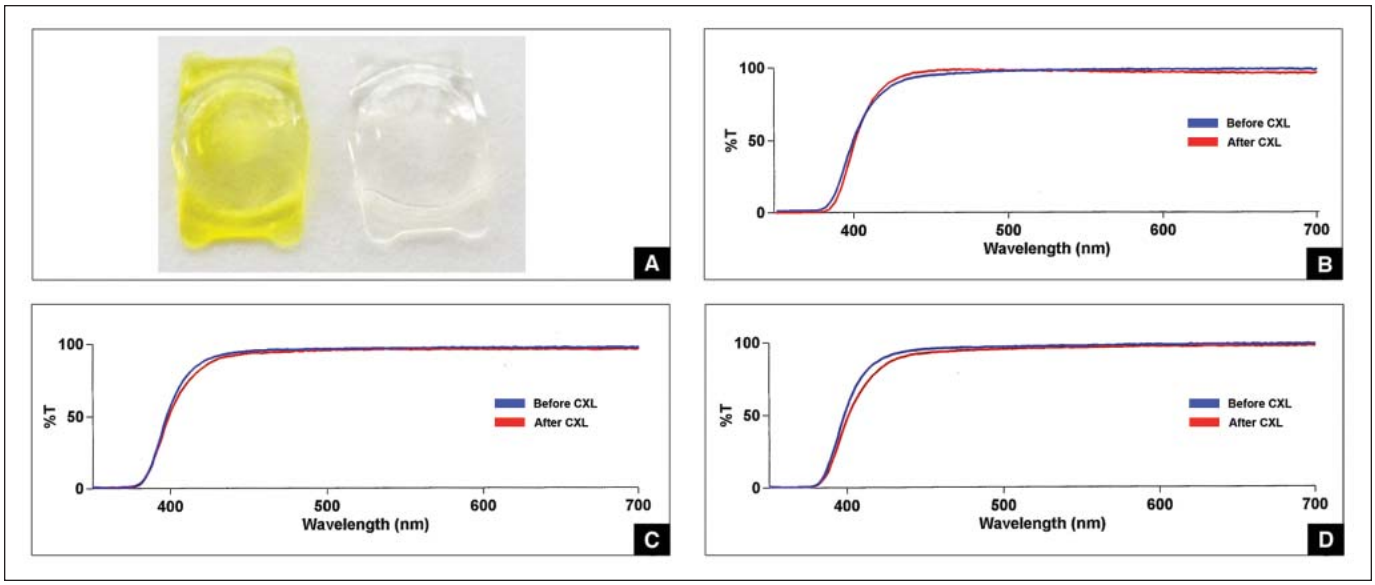

Figure 1. A) Riboflavin wash-out. Macroscopic aspect of the Visian Implantable Collamer Lens (ICL) after 30 minutes of instillation of isoosmolar 0.1% riboflavin solution (left) and at 6 hours after instillation (right). Transmission spectrum before and after cross-linking (CXL) in **B)** control ICLs, **C)** ICLs that were irradiated with 0.23 mW/cm^2, and **D)** ICLs irradiated with 2.3 mW/cm^2. nm = nanometer, %T = percent transmission

expected under actual surgical conditions in humans was calculated under the assumption of a minimal distance between the irradiation device and the ICL. We used the standard irradiation dose of 3 mW/cm^2 and assumed the following conditions: a) a minimal stromal thickness of 400 µm, b) a minimal distance between the ICL and corneal endothelium of 2 mm, and c) a corneal stroma and anterior chamber saturated with 0.1% riboflavin solution. Based on these parameters and using the Lambert-Beer law, the actual dose of UVA irradiation in the plane of the ICL is 0.23 mW/cm^2.

Cross-Linking Procedure

The CXL procedure was performed (F.H.) as follows. Isoosmolar 0.1% riboflavin solution was generated by diluting Vitamin B2-riboflavin-5-phosphate 0.5% (G. Streuli & Co AG, Uznach, Switzerland) with Dextrane T500 20% (Roth AG, Karlsruhe, Germany) (402.7 mOsmol/L). The solution was protected from light and used within 2 hours. Isoosmolar 0.1% riboflavin solution with Dextrane T500 was applied on the ICL every 3 minutes for 30 minutes. After 30 minutes, the ICL was either irradiated for 30 minutes with UVA (UV-X; Peschke Meditrade, Cham, Switzerland) at a working distance of 5 cm with an irradiance of 0.23 mW/cm^2 or 2.3 mW/cm^2 (10× the irradiance dose encountered during actual surgery). During irradiation, isoosmolar 0.1% riboflavin solution was administered every 5 minutes. Control ICLs were placed under the UVA device and were administered isoosmolar 0.1% riboflavin solution every 5 minutes for 30 minutes, but the irradiation was not performed. After irradiation, the lenses were stored in balanced salt solution (BSS).

Dioptric Power Measurement

Two different dioptric strengths of ICLs were chosen for the experiments: −16.00 and −12.00 D. Minus lenses were chosen as they are commonly used in patients with keratoconus. Furthermore, two different dioptric strengths were used to investigate whether the different thickness in the periphery of the optical zone (638 µm and 559 µm) would have an influence on the outcome.

Measurements were performed using the IOLA 2 power measurement system with IOLA software version 2.2.53 (Rolex, Omer, Israel). The IOLA 2 system employs a technology called Moiré Deflectometry. Briefly, a pair of gratings separated by a fixed distance forms a fringe pattern. When the tested lens is inserted in the system, it induces a rotation of the fringe pattern. The system's linear motor is moved until the fringe pattern rotates back to vertical. The displacement of the motor is translated into an initial dioptric power based on a calibration graph built during calibration. The final dioptric power, presented upon conclusion of the measure, is derived from the initial power by including factors such as lens geometry and lens refractive index given as input by the user. Three Visian ICLs were measured at room temperature in a cuvette filled with BSS. The same technician (Eliane Schmid Dionne, Engineer EPFL) took three measurements and values were averaged.

TABLE

Dioptric Power Measurements Before and After Cross-linking With Riboflavin and Ultraviolet A Light

UVA Irradiation (mW/cm^2)	Size (mm)	Center Thickness (mm)	Power (Mean±SD) (D)		Shift (D)
			Before CXL	After CXL	
Control	12.1	0.116±0.10	−16.07±0.01	−16.07±0.01	0.13
Control	12.1	0.116±0.10	−15.96±0.02	−15.96±0.02	0.23
Control	12.1	0.116±0.10	−15.93±0.02	−15.93±0.02	0.26
0.23	12.1	0.116±0.10	−15.92±0.02	−15.92±0.02	0.16
0.23	12.6	0.116±0.10	−12.00±0.02	−12.00±0.02	0.06
0.23	12.6	0.116±0.10	−12.01±0.01	−12.01±0.01	0.01
2.3	12.6	0.116±0.10	−12.02±0.01	−12.02±0.01	0.08
2.3	12.6	0.116±0.10	−11.98±0.01	−11.98±0.01	0.01
2.3	12.6	0.116±0.10	−12.04±0.02	−12.04±0.02	0.07

SD = standard deviation, UVA = ultraviolet A, CXL = cross-linking

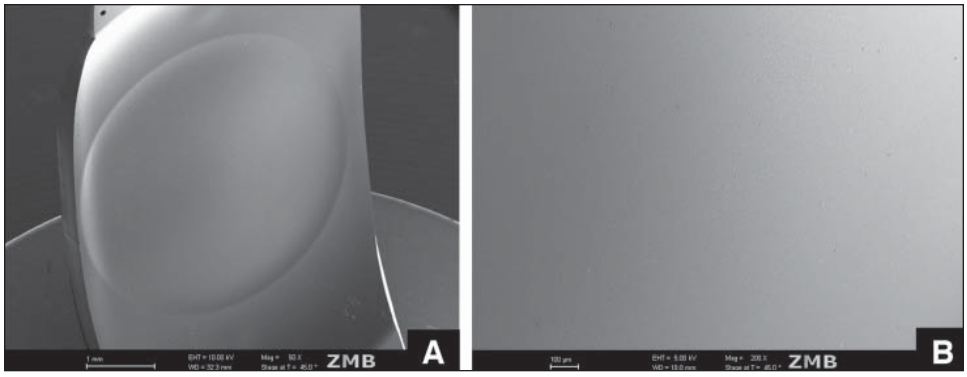

Figure 2. Scanning electron microscopy of the Visian Implantable Collamer Lens following cross-linking (CXL) with 2.3 mW/cm^2 irradiance for 30 minutes. No surface alterations could be observed when analyzing the anterior surface at a magnification of **A)** 50× and **B)** 200× when compared to the surface aspect before CXL (data not shown).

Analysis of the Transmission Spectrum

Transmission curves for nine Visian ICLs were generated in triplicate, and the results were averaged into a single spectral transmission curve for every experimental condition before and after CXL. The UV-visible transmittance spectra were obtained using a Cary 50 spectrophotometer (Varian Inc, Palo Alto, California) by one examiner (F.H.). The percentage transmittance was recorded from 300 to 700 nm in dual beam mode with a data interval of 2 nm at a rate of 9600 nm per minute.

Electron Microscopy

The ICLs were rinsed five times with nanopure water for 20 minutes, air dried for 1 hour at 36.5°C, vertically mounted on aluminium scanning electron microscope stubs using conductive carbon cement, and sputter coated with 5 nm platinum in a SCD 500 sputter coater (Leica Microsystems, Vienna, Austria) using the planetary rotary stage. Samples were imaged in a Zeiss SUPRA 50 VP scanning electron microscope (Gloor Instruments, Uster, Switzerland) using the secondary electron detector by one examiner (Andres Kaech, PhD).

RESULTS

After instillation of 0.1% isoosmolar riboflavin solution for 30 minutes, an intense yellow staining of the Visian ICL was observed. However, similarly to the yellow staining of the cornea observed during CXL in humans, the staining resolved completely within 6 hours (Fig 1A).

Analysis of the dioptric power before and after CXL showed a shift that stayed within the ISO limits of 0.30 D (International Standard on ophthalmic implants, ISO11979-2) for all Visian ICLs investigated (Table). Analysis of the transmission spectrum showed similar curves before and after CXL for all experimental conditions (Visian ICLs treated with 0.23 mW/cm^2, 2.3 mW/cm^2, and controls) (Figs 1B-1D). Examination of the lens surface with a scanning elec-

tron microscope revealed no apparent changes in the surface structure of the Visian ICL before and after CXL for all experimental conditions tested (Fig 2).

DISCUSSION

In this study, we investigated whether CXL with UVA and riboflavin alters the optical and material characteristics of the posterior chamber Visian ICL. To test this hypothesis, we irradiated the Visian ICL in vitro with two different experiments: using the maximal irradiation dose that may be encountered during actual surgery and using 10 times the maximal irradiation dose. Under both experimental conditions, no changes in the optical and material characteristics were observed. The shift in dioptric power following CXL observed was within the tolerance of production and measurements usually accepted for the ICL (±0.30 D). Nevertheless, it is theoretically possible that subtle postoperative CXL changes in the lens material led to the dioptric power changes. The ICL material, however, consists of a proprietary copolymer of porcine-derived collagen and a polymethacrylic base, and the collagen represents only 0.2% to 0.3% of the total material. Collamer has a built-in antireflective coating. In view of the low percentage of (porcine-derived) collagen, it is unlikely that the CXL procedure will affect the optical and material characteristics of the ICL sufficiently to induce changes.

Principally, performing CXL in eyes that had undergone previous implantation of a Visian ICL can be considered safe. However, in a recent study, Vinciguerra et al[19] have shown that CXL significantly reduced the anterior chamber depth (ACD) from 3.42±0.15 mm to 3.28±0.08 mm at 12 months after CXL. An ICL implantation should therefore be performed no earlier than 12 months after CXL, bearing in mind the described slight reduction in ACD.

AUTHOR CONTRIBUTIONS

Study concept and design (F.H., A.D.); data collection (F.H.); analysis and interpretation of data (F.H., F.M.); drafting of the manuscript (F.H.); critical revision of the manuscript (F.H., F.M., A.D.)

REFERENCES

1. Allarakhia L, Knoll RL, Lindstrom RL. Soft intraocular lenses. *J Cataract Refract Surg*. 1987;13(6):607-620.
2. Pineda-Fernández A, Jaramillo J, Vargas J, Jaramillo M, Galíndez A. Phakic posterior chamber intraocular lens for high myopia. *J Cataract Refract Surg*. 2004;30(11):2277-2283.
3. Sanders DR, Doney K, Poco M. United States Food and Drug Administration clinical trial of the Implantable Collamer Lens (ICL) for moderate to high myopia: three-year follow-up. *Ophthalmology*. 2004;111(9):1683-1692.
4. Saxena R, Landesz M, Noordzij B, Luyten GP. Three-year follow-up of the Artisan phakic intraocular lens for hypermetropia. *Ophthalmology*. 2003;110(7):1391-1395.
5. Lackner B, Pieh S, Schmidinger G, Hanselmayer G, Dejaco-Ruhswurm I, Funovics MA, Skorpik C. Outcome after treatment of ametropia with implantable contact lenses. *Ophthalmology*. 2003;110(11):2153-2161.
6. Alfonso JF, Palacios A, Montés-Micó R. Myopic phakic STAAR collamer posterior chamber intraocular lenses for keratoconus. *J Refract Surg*. 2008;24(9):867-874.
7. Kamiya K, Shimizu K, Ando W, Asato Y, Fujisawa T. Phakic toric Implantable Collamer Lens implantation for the correction of high myopic astigmatism in eyes with keratoconus. *J Refract Surg*. 2008;24(8):840-842.
8. Coskunseven E, Onder M, Kymionis GD, Diakonis VF, Arslan E, Tsiklis N, Bouzoukis DI, Pallikaris I. Combined Intacs and posterior chamber toric implantable Collamer lens implantation for keratoconic patients with extreme myopia. *Am J Ophthalmol*. 2007;144(3):387-389.
9. El-Danasoury A. Posterior chamber implantable collamer lens ICL and toric ICL. In: Agarwal A, Agarwal A, Jacob S, eds. *Refractive Surgery*. New Delhi, India: Jaypee Brothers Medical Publishers Ltd; 2009:375-396.
10. Leibowitz, HM, Morello, S. Keratoconus and inflammatory thinning disorders. In: Leibowitz HM, Waring GO III, eds. *Corneal Disorders: Clinical Diagnosis and Management*. Philadelphia, PA: W.B. Saunders Co; 1998:349-374.
11. Hafezi F, Kanellopoulos J, Wiltfang R, Seiler T. Corneal collagen crosslinking with riboflavin and ultraviolet A to treat induced keratectasia after laser in situ keratomileusis. *J Cataract Refract Surg*. 2007;33(12):2035-2040.
12. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. *J Cataract Refract Surg*. 2008;34(5):796-801.
13. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen cross-linking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135(5):620-627.
14. Hafezi F, Dejica P, Majo F. Modified corneal collagen cross-linking (CXL) reduces corneal oedema and diurnal visual fluctuations in Fuchs dystrophy. *Br J Ophthalmol*. 2010;94(5):660-661.
15. Iseli HP, Thiel MA, Hafezi F, Kampmeier J, Seiler T. Ultraviolet A/riboflavin corneal cross-linking for infectious keratitis associated with corneal melts. *Cornea*. 2008;27(5):590-594.
16. Hafezi, F, Marti A, Munz K, Remé CE. Light-induced apoptosis: differential timing in the retina and pigment epithelium. *Exp Eye Res*. 1997;64(6):963-970.
17. Hafezi F, Steinbach JP, Marti A, Munz K, Wang ZQ, Wagner EF, Aguzzi A, Remé CE. The absence of c-fos prevents light-induced apoptotic cell death of photoreceptors in retinal degeneration in vivo. *Nat Med*. 1997;3(3):346-349.
18. Grimm C, Wenzel A, Williams T, Rol P, Hafezi F, Remé C. Rhodopsin-mediated blue-light damage to the rat retina: effect of photoreversal of bleaching. *Invest Ophthalmol Vis Sci*. 2001;42(2):497-505.
19. Vinciguerra P, Albè E, Trazza S, Rosetta P, Vinciguerra R, Seiler T, Epstein D. Refractive, topographic, tomographic, and aberrometric analysis of keratoconic eyes undergoing corneal cross-linking. *Ophthalmology*. 2009;116(3):369-378.