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ORIGINAL ARTICLE

Five Years Follow-up of Riboflavin/Ultraviolet A (370 nm) Corneal Collagen Cross-linking to Halt the Progression of Keratoconus

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ABSTRACT

Aims: To determine the long-term efficacy and safety of riboflavin/ultraviolet a corneal cross-linking (CXL) to halt the progression of keratoconus.

Materials and methods: Thirty-five patients (35 eyes) who had undergone CXL with epithelial removal 5 or more years previously were examined.

Results: At 5 years, mean spherical equivalent (SEQ) increased by 0.78 diopters (D) ($p < 0.001$), mean simulated K (Sim K) reduced by 0.86D ($p < 0.00001$), cone apex power (CAP) reduced by 1.1D ($p < 0.0002$) and root mean square (RMS) ($p < 0.0001$), coma ($p < 0.0001$), and secondary astigmatism ($p < 0.001$) decreased compared to preoperative values. Compared to values at 1 year, mean refractive cylinder reduced by 0.26D ($p < 0.05$), mean Sim K reduced by 0.46D ($p < 0.0005$), CAP reduced by 0.81D ($p < 0.01$), RMS ($p < 0.001$), coma ($p < 0.002$) and secondary astigmatism ($p < 0.02$) reduced and central pachymetry increased ($p < 0.05$) at 5 years. No treated eyes showed evidence of progression at 5 years. None lost >1 line of CDVA. Eight untreated fellow eyes progressed during the follow-up period and underwent CXL.

Conclusions: Corneal cross-linking is an effective treatment to halt the progression of keratoconus at 5 years, with no sight-threatening complications. Improvements in topographic and wave-front indices present at 1 year continue to improve at 5 years.

Keywords: Keratoconus, Cross-linkage, Riboflavin, Ultraviolet light.

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INTRODUCTION

Riboflavin/ultraviolet corneal collagen cross-linking (CXL) is the first treatment modality that appears to halt the progression of keratoconus.[1] Although its precise mechanism of its action and actual sites of molecular cross-links is as yet undetermined, laboratory studies have shown CXL to increase corneal stromal extensiometry measurements and reduce its resistance to enzymatic digestion and thermal damage.[2-5] Two seminal clinical studies demonstrated stabilization of ectasia with no reduction in corneal transparency and an improvement in keratometric indices[6,7] and subsequent multiple prospective studies have confirmed these favorable results.[8,9] In one of the few randomized, prospective studies we have reported CXL to be both effective and safe in halting the progression of keratoconus and enhancing visual, topographic and wave-front parameters in treated eyes, with progression being documented in a number of untreated eyes over an 18 months follow-up period.[10]

Whilst published clinical studies support the efficacy this new procedure, there is as yet a scarcity of long-term follow-up data. Keratoconus characteristically evolves in erratic manner for up to twenty years following its manifestation and then tends to stabilize, presumably as a result of physiological age-related cross-linking.[11] The turnover rate of corneal collagen and the extracellular matrix (ECM) is unknown and the requirement to possibly repeat CXL is undetermined. Only a few groups have actually presented data with over 3 to 4 years follow-up. Raiskup-Wolf et al reported 33 eyes with over 3 years follow-up and found stabilization of keratoconus with reduction of keratometry and improvements in vision.[12] Caporossi et al detected keratoconus stability in 44 eyes after 48 months, with a reduction in keratometry and coma and improvements in vision.[13] We in a series of 30 eyes with over 4 years follow-up found keratoconic stabilization in all eyes, with significant improvements in refraction, visual acuity, keratometry and corneal wave-front measurements.[14] In addition and similar to the findings of Raiskup-Wolf et al[12] they documented continued improvements in keratometry and higher order aberrations with follow-up. The aims of this study were to present further data on the long-term efficacy. We report 35 eyes of 35 patients, who underwent epithelium-off CXL with over 5 years follow-up.

MATERIALS AND METHODS

Subjects

All subjects who underwent CXL at our institution over 5 years previously were invited to return for an ophthalmic examination. Thirty-five patients from a cohort of 41 attended (4 patients were lost to follow-up, one had died from an unrelated neoplastic illness and one who had achieved refractive and topographic stability 24 months after CXL elected to undergo intrastromal ring segment insertion). Mean age at time of CXL was 26.6 years (12-40, median 25 years). Thirty patients were males, 5 were females. One eye of each patient was selected for analysis. Twenty-five had only one eye treated. In two cases, the fellow eye was unsuitable for CXL because of advanced disease and underwent deep anterior lamellar keratoplasty. In one case, the fellow eye had undergone intrastromal ring segment insertion. In 2 patients bilateral simultaneous CXL had been performed. In these individuals, one eye was selected randomly for analysis, using an independent observer with a shuffled envelope system. In the remaining 8 cases, CXL was performed in the contralateral eye 18 to 48 months after treatment of the first. In these individuals the first eye treated was selected for analysis.

All treated eyes had early to moderate keratoconus (grade I to III according to Amsler-Krumeich's classification, with mean keratometry readings of less than 56 (D), absence of corneal scarring and minimum corneal thickness of greater than 400 μm) with documented evidence of progression with reduced uncorrected distance (UDVA) or corrected distance visual acuity (CDVA) by > 1 line and/or worsening of refractive or corneal astigmatism, keratometry or cone apex power (CAP) by 0.75D over the 12 to 24 months prior to CXL.

Exclusion criteria included advanced keratoconus where corneal irregularity/scarring prevented acquisition of accurate refractive and topographic data, central corneal thickness less than 400 μm (with epithelium on), other ocular pathology, previous anterior segment surgery and diabetes.

Prior to CXL, subjects were counselled as to the nature of the procedure. An ophthalmic and medical history was taken, including refractive and contact lens history, past ophthalmic and family history. Patients were asked to refrain from rigid lens wear for 3 weeks and soft lens wear for 1 week prior to ophthalmic examinations.

Objective and subjective refraction, Snellen decimal equivalent UDVA and CDVA, scanning-slit corneal topography (Orbscan II, Bausch and Lomb, Germany) and Placido-disc videokeratography (Keraton Scout Corneal Analyzer, Optikon 2000, Rome, Italy), ultrasonic central corneal pachymetry (Pachmate DGH55, DGH Technology Inc., PA, USA), slit-lamp biomicroscopy, tonometry and mydriatic fundoscopy were performed. For Orbscan examinations, 2 scans for each eye were taken and the average of values calculated. For Keraton Scout examinations, 4 scans for each eye were taken and the highest quality scan closest to the average keratometry values was selected for wavefront analysis and CAP measurement. CAP was determined using the cone location and magnitude index (CLMI).[15]

Surgical Procedure

We have described this procedure previously,[10,14] which was based on the original protocol described by Wollensak et al.[6] Following informed consent, tetracaine 1% and Chloramphenicol 0.5% were instilled. A 9.00 mm area of central epithelium was removed using a disposable corneal epithelial spatula (Malosa Medical, Elland, UK). Five drops of riboflavin 0.1%, in dextran 20% were instilled. A period of 5 to 10 minutes elapsed before UVA exposure. UVA exposure was for 30 minutes and utilized 370 nanometer (nm) UVA radiation at 3 milli-Watts per centimeter squared (mW/cm^2) with a beam diameter of 8.00 mm. During UVA exposure, riboflavin 0.1% drops were administered every 3 to 5 minutes and tetracaine 1% drops if the patient reported discomfort.

Postoperative Treatment and Assessment

Following surgery, Ofloxacin 0.3% and chloramphenicol 1% were administered and the eye padded. Oral analgesics, Ibuprofen 400 mg PRN tds and codeine phosphate 30 to 60 mg PRN qds, were prescribed. Four vials of Benoxinate 0.4% were given, with instructions to be administered if the postoperative pain was severe and with a maximum dosage of 1 drop only every 2 hours for a maximum of 48 hours. Ofloxacin 0.3% eye were administered 4 times a day for 1 week and chloramphenicol 1% ointment at night for 2 weeks.

Postoperative examinations were conducted at regular intervals including at 1 week and at 1, 3, 6, 12 months and 5+ years. Patients were questioned concerning ophthalmic symptoms and an examination was performed, including UDVA, CDVA, refraction, Placido-disk and scanning-slit topography, corneal pachymetry, slit-lamp biomicroscopy, tonometry and mydriatic fundoscopy.

Vector Analysis

To investigate astigmatic change in the manifest refraction, vector analysis was performed according to the system described by Retzlaff et al.[16]

Statistical Methods

Paired student t-tests were used to compare pre- and postoperative outcomes within the treated and untreated groups.

Table 1: Pre- and 1 and 5 years postoperative results (±1 standard deviation) in 35 study eyes

Parameter	*Preoperative*	*12 months*	*4-6 years*	**p-value*	***p-value*
SEQ	–1.46 ± 1.89D	–0.93 ± 1.7D	–0.68 ± 1.63D	<0.005	0.2
Refractive cylinder	–3.32 ± 2.43DC	–3.39 ± 2.51DC	–3.12 ± 2.31DC	0.5	<0.05
UCVA (LogMAR)	0.56 ± 0.32	0.54 ± 0.36	0.53 ± 0.33	0.5	0.9
BSCVA (LogMAR)	0.09 ± 0.17	0.04 ± 0.12	0.05 ± 0.11	0.06	0.9
Pachymetry	487 ± 36 µm	486 ± 36 µm	490 ± 38 µm	0.5	<0.04
Mean Sim K	46.42 ± 3.4D	46.02 ± 3.26D	45.6 ± 3.2D	<0.0001	<0.001
Corneal topographic astigmatism	3.85 ± 2.37D	3.73 ± 2.94D	3.55 ± 1.97D	0.3	0.2
Cone apex power	51.37 ± 4.48D	51.08 ± 4.26D	50.27 ± 4.42D	<0.0002	<0.01

*p-values at 5 years compared to preoperative values, **p-values at 5 years compared to 1 year values
Refractive, visual and topographic parameters

Visual acuity results were coverted into LogMAR values before averaging and statistical calculation. Results $p < 0.05$ were considered significant.

RESULTS

Spherical Equivalent Refractive Error

Preoperatively, the mean SEQ in the study eyes was –1.46D. At 12 months, it reduced to –0.92D ($p < 0.005$). At 5 years, it reduced to –0.68DD ($p < 0.0005$). There was no statistically significant difference in SEQ at 12 months and 5 years ($p = 0.2$) (Table 1).

In 30 fellow eyes that were suitable for CXL but initially remained untreated, the mean SEQ was –1.83D at first examination and –1.91D at 18 to 65 months ($p = 0.6$).

Refractive Cylindrical Correction

Preoperatively, the mean cylindrical error in study eyes was –3.32DC at 850. At 12 months, it was –3.39DC at 880 ($p = 0.6$). At 5 years it was –3.12DC at 800, which was unchanged compared to preoperative ($p = 0.5$) but less than 12 months values ($p = 0.05$) (Table 1). Vector analysis at 5 years compared to preoperative measurements demonstrated a mean 1.99D change.[16]

In 30 fellow eyes that were suitable for CXL but remained initially untreated, the mean cylindrical error was –2.5D at 950 at the first examination and –3.31D at 950 at 18 to 65 months ($p < 0.0002$). Vector analysis demonstrated a mean 2D change.

Visual Performance

Uncorrected Distance Visual Acuity

Preoperatively, the mean LogMAR UDVA in the study eyes was 0.56. At 12 months, it was 0.54 ($p = 0.7$). At 5 years, it was 0.53 ($p = 0.5$) (Table 1).

At first examination, the mean LogMAR UDVA in 30 initially untreated eyes was 0.59. At 18 to 65 months, it was 0.6 ($p = 0.6$).

Corrected Distance Visual Acuity

Preoperatively, the mean LogMAR CDVA in the study eyes was 0.09. At 12 months, it had increased to 0.04 ($p = 0.03$). At 5 years it was 0.05, which was not significantly increased compared to preoperative values ($p = 0.06$) and unchanged from 12 months ($p = 0.9$) (Table 1).

At first examination the mean LogMAR CDVA in the 30 initially untreated eyes was 0.06. At 18 to 65 months, it was 0.06 ($p = 0.8$).

Corneal Pachymetry

Preoperatively, the mean pachymetric measurement in the study eyes was 488 micrometers (µm). At 12 months, it was unchanged at 486 µm ($p = 0.2$). At 5 years, it was 490 µm, which was not significantly changed from preoperative values ($p = 0.5$), but increased from 12 months measurements ($p < 0.04$) (Table 1).

At first examination the mean pachymetric measurement in the 30 initially untreated eyes was 492 µm. At 18 to 65 months, it was unchanged at 493 µm ($p = 0.7$).

Corneal Topography

Preoperatively, the mean simulated keratometry (Sim K) in study eyes was 46.42D. At 12 months, it had reduced to 46.02D ($p < 0.04$) (range of change –1.53 to +1.05D, median –0.24D). At 5 years it was reduced to 45.66D which was less than preoperative values ($p < 0.00001$) (–4.65 to +0.75, median –0.71) and 12 month measurements ($p < 0.0005$) (–3.4 to +0.61D, median –0.5D) (Table 1).

Preoperatively, the mean simulated corneal topographic astigmatism in study eyes was 3.82D. At 12 months, it was 3.73D ($p = 0.7$). At 5 years it was 3.56D ($p = 0.2$) (Table 1).

Preoperatively, mean CAP in the study eyes was 51.4D. At 1 year, it was reduced to 51.1D ($p < 0.005$) (–2.78 to 1.35D, median –0.5D). At 5 years, it was reduced to 50.27D, which was less than preoperative values ($p < 0.0002$) (–4.14 to 0.56D, median –1.0D) and those at 12 months ($p < 0.01$) (–2.42 to 1.16D, median –0.57D) (Table 1).

Table 2: Pre- and 1 and 5 year postoperative results (±1 standard deviation) in 35 study eyes

Parameter	*Preoperative (μm)*	*12 months (μm)*	*4-6 years (μm)*	**p-value*	***p-value*
Root mean square	2.44 ± 1.19	2.44 ± 1.13	2.19 ± 1.06	<0.0005	<0.0005
Coma	2.07 ± 1.2	2.12 ± 1.12	1.82 ± 1.11	<0.001	<0.002
Trefoil	0.81 ± 0.41	0.79 ± 0.33	0.82 ± 0.33	0.8	0.7
Spherical aberration	0.19 ± 0.45	0.18 ± 0.44	0.2 ± 0.37	0.4	0.2
Secondary astigmatism	0.58 ± 0.34	0.51 ± 0.28	0.45 ± 0.26	<0.001	<0.02
Quatrefoil	0.27 ± 0.2	0.22 ± 0.13	0.21 ± 0.11	0.5	1.0
Secondary coma	0.27 ± 0.2	0.26 ± 0.2	0.25 ± 0.16	0.1	0.4
Secondary trefoil	0.15 ± 0.1	0.13 ± 0.1	0.14 ± 0.09	0.3	1.0
Pentafoil	0.08 ± 0.05	0.07 ± 0.05	0.06 ± 0.04	0.06	0.6

*p-values at 5 years compared to preoperative values, **p-values at 5 years compared to 1 year values
Corneal wave front higher order aberations

In 30 initially untreated eyes, at first examination the mean Sim K was 45.74D. At 18 to 65 months it was 46.23D ($p < 0.05$). At first examination, the mean simulated astigmatism in was 2.87D. At 18 to 65 months, it was 3.18D ($p = 0.7$). At first examination, the CAP was 52.16D. At 18 to 65 months, it was 52.92D ($p = 0.1$).

Corneal Wavefront Measurements

Higher order aberrations of the anterior corneal surface for a 6.0 mm pupil diameter preoperatively, at 12 months and 5 years for the 35 study eyes are shown in Table 2. Secondary astigmatism was reduced at 12 months compared to preoperative values ($p < 0.03$). At 5 years root mean square values (RMS) ($p < 0.0001$), coma ($p < 0.0001$) and secondary astigmatism ($p < 0.001$) were reduced compared to preoperative values. RMS ($p < 0.001$), coma ($p < 0.002$) and secondary astigmatism ($p < 0.02$) were reduced at 5 years compared to 1 year values.

In the 30 initially untreated eyes spherical aberration became more negative over the follow-up period of 18 to 625 months ($p = 0.002$).

Improvement/progression of Ectasia

Twelve study eyes (34%) showed evidence of reduction of ectasia at 48 to 72 months, identified on the basis of both a decrease in Sim K and CAP of >1D and improvements in other refractive, visual, topographical and keratometric parameters. Six of 30 initially untreated eyes (20%) demonstrated evidence of progression, with an increase in both Sim K and CAP of >1.0DD and consistent worsening of other measurements at 18 to 65 months follow-up and underwent. No study eyes appeared to show evidence of progression, with none showing an increase in either Sim K or CAP of >0.75D at 5 years.

Complications

There were no changes in transparency of the cornea or lens. All retinal examinations were normal. At 5 years in study eyes, CDVA was increased in by 2 lines in 6 eyes (17%), 1 line in 5 eyes (14%), was unchanged in 19 eyes (54%) and reduced by 1 line in 5 eyes (14%). No eyes lost >1 line. One untreated eye lost 2 lines of BSCVA.

DISCUSSION

Corneal cross-linking is the only treatment currently available that can arrest the progression of keratoconus and other corneal ecstatic disorders. Multiple prospective clinical studies support its efficacy.[7-10,12-14,17-19] While, however, the effectiveness of CXL has been documented over the medium term, its long-term efficacy is unsure. Keratoconus typically manifests in adolescence, progresses for a few decades and then typically stabilizes, presumably as natural age-related cross-linking of the cornea occurs.[20] It is a heterogeneous disorder, with varying morphological characteristics and unpredictable rates of progression.[20] The turnover rate of corneal structural macromolecules is as yet undetermined. Therefore the length of efficacy of CXL and the necessity to repeat it if late progression occurs is unsure and continued long-term follow-up is essential.

As yet there is still a paucity of long-term follow-up data in the literature. Raiskup-Wolf reported a cohort 33 eyes with over 3 years follow-up. They documented stabilization of ectasia in 98% of cases with further improvements in keratometric and visual parameters time.[12] Caporossi et al reported stability of keratoconus in 44 eyes after 4 years, with improvements in keratometry, wave-front and visual acuity indices.[13] We in a cohort of 30 eyes with follow-up over 4 years found stability in all cases and similar to Raiskup-Wolf continued and statistically significant reductions in topographic and corneal wave-front values at 4 years compared to 1 year.[13] This current study, which represents a continued follow-up of our cohort with inclusion of further cases, confirms our initial results. It confirms not only the efficacy and safety of CXL in halting the keratoconic process but continued improvement of the irregular corneal shape with time.

Our results and those of Raiskup-Wolf and Caparossi et al, signify that epithelium–off CXL is effective in arresting the progression of keratoconus for at least 4 to 6 years. Further follow-up will further elucidate the long-term efficacy and the need if any to repeat the procedure and how long and to what degree eyes might continue with improvement in visual and topographic parameters. The reappearance of keratoconus following penetrating keratoplasty, which may occasionally occur 1 to 2 decades after surgery following surgery,[20,21] intimates that the turnover of corneal collagen and ECM may be measured in decades. CXL might therefore be effect for at least this length of time if not longer given physiological cross-linking changes that occur naturally with age.

Although most eyes are stabilized after CXL, failure of treatment with progression of ectasia can occur. Koller et al in 177 eyes, reported progression in 8 cases (7.6%) and identified eyes with advanced keratoconus with maximum keratometry values >58D of being at greatest risk.[22] In this study, no treated eyes progressed with over 5 years follow-up. However, only eyes with grade I to III according to Amsler-Krumeich's classification were included and none had mean Sim K values greater than 56D. This present study cannot therefore reveal the possible long-term stability of CXL in cases of advanced keratoconus where given the more aggressive and advanced nature of the disease and greater biomechanical impairment, efficacy and stability of CXL might not perhaps be so encouraging.

A remarkable finding of our study was the continued of improvement of visual, wave-front and topographic parameters with time (Table 1). An amplified activity of proteinase enzymes and diminished action of proteinase inhibitors has been recognized in keratoconus.[23] Such changes may result in augmented stromal protein digestion, which may be liable for corneal thinning and subsequent reduction in biomechanical stability.[24] It can be postulated that cross-linking of corneal collagen and ECM reduces the efficacy of these proteinase enzymes, reducing stromal protein digestion while the laying down of new collagen and ECM continues as part of normal physiological processes. This could results in improvement in corneal biomechanics and shape and an increase in corneal thickness, as identified in our study between 1 and 5 years. The documentation of increased resistance of cross-linked corneal tissue against enzymatic digestion by Spoerl would support this hypothesis.[4] It is important to note that whilst no treated eyes appeared to progress, 20% of initially untreated fellow eyes in our study demonstrated evidence of progression. As well as further supporting the efficacy of CXL, such changes indicate that improvements in measured parameters with time are not due to physiological age-related cross-linking changes.

There were no sight-threatening complications in this long-term study. Corneal transparency was maintained. No eyes lost more than one line of CDVA and over 30% gained lines. There was no evidence of damage to internal ocular structures such as the endothelium, lens and retina, which given the very limited total UVA dosage required for CXL is what is expected.

Epithelium-off Riboflavin/UVA CXL appears to be both an effective and safe modality to arrest the progression of keratoconus with up to 5 years follow-up. Improvements in topographic and wave-front indices evident at 1 year continue to improve at 5 years. However, further follow-up is indicated given chronic nature of keratoconic progression to determine the long-term efficacy of the procedure and the need to repeat it if necessary.

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