FACULDADE DE MEDICINA DA UNIVERSIDADE DE COIMBRA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

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Multimodal assessment of functional and structural retinal changes in patients undergoing accelerated corneal collagen cross-linking

ARTIGO CIENTÍFICO

ÁREA CIENTÍFICA DE OFTALMOLOGIA

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MAIO 2017

Índice

ABSTRACT

Purpose: The purpose of our study was to assess the functional and structural retinal changes in consecutive patients undergoing accelerated corneal collagen cross-linking.

Methods: Our study population consisted in ten eyes of 10 consecutive keratoconus patients. All participants underwent a complete ophthalmological examination before surgery. Structural characterization of the central retina by OCT and OCT-A was obtained before surgery and 1 week and 1 month after surgery. Functional assessment of retinal function was performed with microperimetry, before surgery and 1 month post-operatively.

Results: No retinal changes consistent with photic maculopathy were observed on any of the eyes enrolled. Central retinal vascular density and vascular flow showed no significant change after surgery. There was no obvious overall difference between pre and post-operative macular function, as measured by microperimetry.

Conclusion: Our study showed no evidence functional and structural retinal changes consistent with photic maculopathy in patients undergoing accelerated corneal collagen cross-linking treatment.

INTRODUCTION

Keratoconus is a slowly progressive noninflammatory corneal ectatic condition, unilateral or bilateral asymmetric and is characterized by corneal thinning and protrusion, progressive myopia and astigmatism. The latest studies show a prevalence ranging from 50 and 600 in 100.000 individuals in the general population[1] affecting predominantly young and active individuals. It is considered a major condition affecting the quality of life and life

planning.

The introduction of Collagen cross-linking (CXL) represented a breakthrough in the approach to keratoconus treatment.[2] CXL is therapeutic technique that requires stromal absorption of riboflavin followed by ultraviolet A (UVA) exposition. The final aim is to slow or halt the progression of the disease in its early stages, ultimately delaying or avoiding keratoplasty.[3,4] In conventional CXL, also known as the "Dresden Protocol", patients are instructed to stare for 30 minutes into a UVA (370 nm) irradiation source with an intensity of $3mW/cm^2$, to deliver a cumulative energy dose of $5.4J/cm^2$ to the eye.[3] Early model studies showed that, due to riboflavin block, classic CXL irradiance was below the threshold for retinal damage.[2] A recently proposed alternative**,** accelerated corneal Collagen cross-linking (ACXL) can speed up the procedure by delivering a much higher intensity of irradiation to allow for a simultaneous marked reduction of treatment time.[5]

The human retina is designed to absorb photons. Prolonged exposure to intense light sources is known to cause photochemical changes to the retina, potentially resulting in cell death, even with light levels at or below those specified by currently published safety standards.[6] In fact, retinal light damage is a well known complication of numerous daily ophthalmologic procedures, ranging from exposure to prolonged slit-lamp examination[7] to countless reports of light damage resulting from cataract surgery [8,9] and vitreo-retinal surgery.[10] In studies designed to address this possibility, its incidence was as high as 8.47%[11] or 28%.[12]

It is reasonable to assume that the higher intensity of irradiation used in ACXL may result in some level of retinal photobleaching. Most safety reports on ACXL focus on corneal side effects alone (corneal haze, infections, endothelial damage) and omit the potential for iatrogenic retinal phototoxicity.[13]

To our knowledge this is the first study aimed at systematically exploring the retinal response to ACXL-related UVA irradiation. For that purpose, we decided to perform serial multimodal assessment of functional and structural retinal changes in consecutive patients undergoing ACXL.

MATERIAL AND METHODS

Population

This prospective, consecutive, clinical study was conduced in compliance with the institutional and government review board regulations. Written informed consent was obtained from all patients. This study adhered to the tenets of the declaration of Helsinki.

Ten eyes of 10 consecutive keratoconus patients were recruited from the Cornea clinic at the Department of Ophthalmology of the Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal.

The key inclusion criteria for the study was documented progression of keratoconus in the last year. Patients in all Amsler-Krumeich stages (I to IV) were included. Progression was defined as: front maximal or mean keratometry steepening of >1 diopter (D); decrease in central corneal thickness >5% or 20 μm; increase of posterior elevation >15 μm; increase of manifest myopia, astigmatism or spherical equivalent >1 D; or decrease of one Snellen line of best corrected visual acuity. A minimal corneal pachymetry of 400 μm was required.

Exclusion criteria were (1) previous intraocular or corneal surgery, (2) pregnancy or lactation, (3) any other signs of corneal or anterior segment pathology, (4) presence of any known retinal disease, and (5) any treatment with an ocular or systemic investigational agent in the past 60 days for any medical condition.

Surgical procedure and follow-up

All patients performed ACXL using the same riboflavin solution (Vibex Rapid®, Avedro, Waltham, MA, USA) and the same UVA device (KXL System®, Avedro, Waltham, MA, USA). After a 10-minute soak, with application of drops every 2 minutes, the patients underwent UVA irradiation protocol deploying 30 mW/cm for 8 minutes with pulsed light 1 second on/1 second off.

All surgeries were performed in the operating theatre under sterile conditions. The ocular surface was anesthetized with topical oxybuprocaine hydrochloride 0.4%. The corneal epithelium was marked with a sterile surgical marker and removed in the 9.0 mm treatment zone using a disposable blade knife. The cornea was impregnated with riboflavin for 10 minutes, as per the manufacturer's instructions. Subsequently, the cornea was exposed to UVA without rinsing. After treatment, the corneal surface was rinsed with balanced salt solution.

Postoperatively, all patients received oral analgesia (clonixin 300 mg up to three times daily, for 3 days), topical fluoroquinolone eye drops for a week and artificial tear drops for a month. After complete epithelium healing, corticosteroid eye drops (flurometholone acetate 0.1%) were started 4 times daily for a week and tapered over three months.

Follow-up check-ups were performed on the first day, seventh day and first month after the operation.

Retinal assessment

Optical Coherence Tomography Angiography

Optical Coherence Tomography Angiography (OCT-A) is a new technology with great potential for use in the clinical setting, providing a noninvasive OCT-based method for visualizing the vascular structures of the retina.

The Optovue RTVue XR Avanti AngioVue software uses the split-spectrum amplitude decorrelation angiography (SSADA) algorithm. This instrument has a 70 kHz axial scan repetition rate, using a light source centered on 840 nm and a bandwidth of 50 nm. The optical axial resolution is 5 µm, and the transverse is 15 µm. Each OCT-A volume contains 304 x 304 A-scans with two consecutive B-scans (M-B frames) captured at a fixed position before proceeding to the next sampling location. The volumes were registered and the B-scan images were compared to calculate the decorrelation in the images along with motion artefact removal. In addition, the OCT-A device is capable of acquiring the standard structural SD-OCT scans typically used by other commercially available devices. This allowed us to assess concurrently retinal blood flow and overall retinal structure.

For this report the scanning area was captured in 3x3 mm sections and was centered on the fovea.

Microperimetric assessment

Microperimetry was performed using the Nidek MP1 (NAVIS software version 1.7.1-Nidek Technologies). This instrument allows the examiner to view the fundus on the computer monitor while it is imaged in real time by an infrared (IR) fundus camera (768 × 576 pixels' resolution; 45° field of view).

Fixation target and stimuli are projected onto the liquid crystal display (LCD) within the MP1 for the subject to view. The examiner can also view the overlaid graphic of the threshold values and fixation loci as part of the video IR image on the computer monitor. Background luminance is set at 1.27 cd/m2 (white, within the high-mesopic range). Stimulus intensity can be varied in 1-dB (0.1 log) steps from 0 to 20, where 0 dB represents the brightest luminance of 127 cd/m2. The MP1 also incorporates an automated tracking system to compensate for eye movement during examination.

An infrared image of the fundus is captured immediately before the examination to allow areas with high contrast (e.g., large vessels, disc margin, or pigmented lesions) to be chosen for tracking. This reference landmark is tracked every 40 ms (25 Hz) to allow correction of the stimulus position on the internal LCD to maintain the same test locations on the fundus.

Data statistical analysis

The numerical data extrapolated from all procedures were entered in SPSS statistics software, v24.0. All values are presented as mean±SD for continuous variables and as absolute value and percentage for discrete variables.

The Related-Samples Wilcoxon Signed Rank Test was used to compare preoperative and postoperative data. The significance value was set at 0.05.

RESULTS

Baseline population

We enrolled 10 consecutive patients performing ACXL for this study. The reason for surgery was progressive keratoconus on all cases. The mean age at the time of ACXL surgery

was 21.70 ± 6.38 years (range 15-34 years). Out of the 10 patients enrolled, 6 patients were male and 4 were female. The comprehensive preoperative patient data is presented on **Table 1**.

Table 1. Preoperative Patient Data

Parameter	
Eyes/patients (n)	10/10
Sex (male/female)	6/4
Age (mean±SD)	21.70 ± 6.38
Range	15 - 34
Kmax (D) Mean±SD	54.09 ± 3.18
Range	50.50 – 59.8
Kmean (D) Mean±SD	51.77 ± 4.00
Range	46.95 – 58.65
Kmin (D) Mean±SD	49.45 ± 5.14
Range	43.40 - 57.5
UCVA (Snellen) Mean±SD	0.18 ± 0.10
Range	0.05 – 0.3
BSCVA (Snellen) Mean±SD	0.37 ± 0.17
Range	0.1 – 0.6
SE (D) Mean±SD	-3.69 ± 2.97
Range	(-1.50) - (-8.50)
Refractive astigmatism (D) Mean±SD	3.46 ± 2.03
Range	1.25 - 6.00
Thinnest (mm) Mean±SD	455.40 ± 22.94

OCT-A Assessment

All OCT-A images were qualitatively reviewed by two independent observers. As expected, all pre-operative OCT-A were deemed normal and all patients were considered proper models for the study. Serial OCT-A were performed at 1 week and 1 month after surgery and were assessed for the presence of any changes deemed consistent with phototoxic damage. Special attention was reserved to the outline of foveal B-scans, in search of known hallmark alterations of phototoxic retinopathy, namely foveal thinning, vertical hyper-reflective bands, ellipsoid and external limiting membrane disruption, and hyporeflective cavities. On all patients, corneal clarity was sufficient to allow for satisfactory image acquisition, including on 1-week post-operative images. No consistent suspected changes were observed on any of the patients enrolled. An example of a patient is outlined on **Figure 1**.

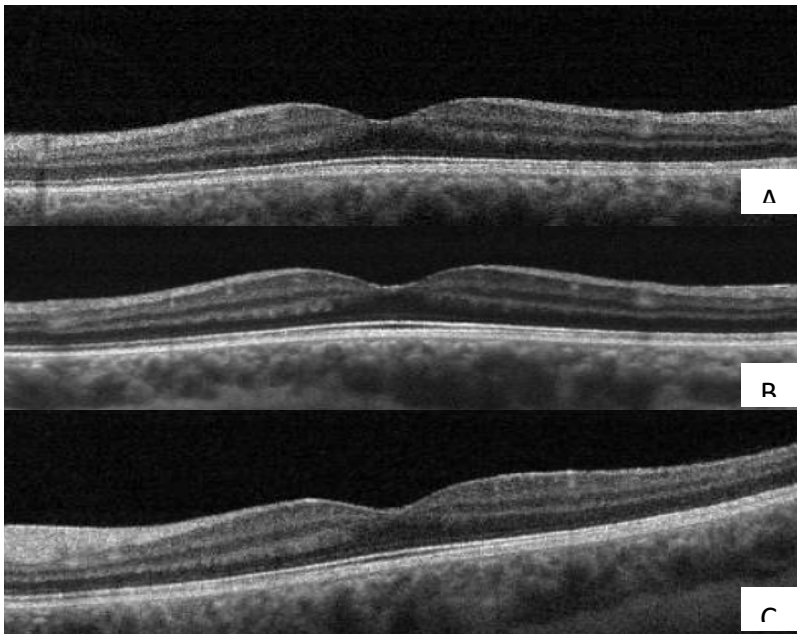

Figure 1. Foveal display of patient obtained before surgery (A) and 1 week (B) and 1 month (C) after ACXL. Notice the normal foveal outline across all time points considered and the absence of any outer retinal changes compatible with photochemical damage.

OCT Angiography

Vessel Density

Mean vessel density was automatically calculated for the whole image and the sectors predetermined by the proprietary software **(Figure 2)**.

Mean vessel density values for the baseline images and the post-operative serial evaluations are displayed in **Table 2**.

Table 2

% (p)	Baseline	1 Week	1 Month
Whole Image	49.08	48.66 (0.50)	48.00 (0.50)
Foveal	32.77	34.50 (0.23)	35.81 (0.50)
Parafoveal	49.38	50.03 (0.89)	46.08 (0.225)
Superior Hemifield	49.13	50.09 (0.52)	46.43 (0.138)
Inferior Hemifield	49.64	48.72 (0.69)	47.13 (0.99)
Superior	50.40	48.89 (0.86)	46.45 (0.200)
Inferior	48.76	50.49 (0.80)	46.24 (0.209)
Nasal	48.63	50.64 (0.84)	46.11 (0.345)
Temporal	49.82	51.30 (0.76)	47.40 (0.248)

Vessel density is displayed as the mean of all exams. Comparison was made using the Wilcoxon signed rank test

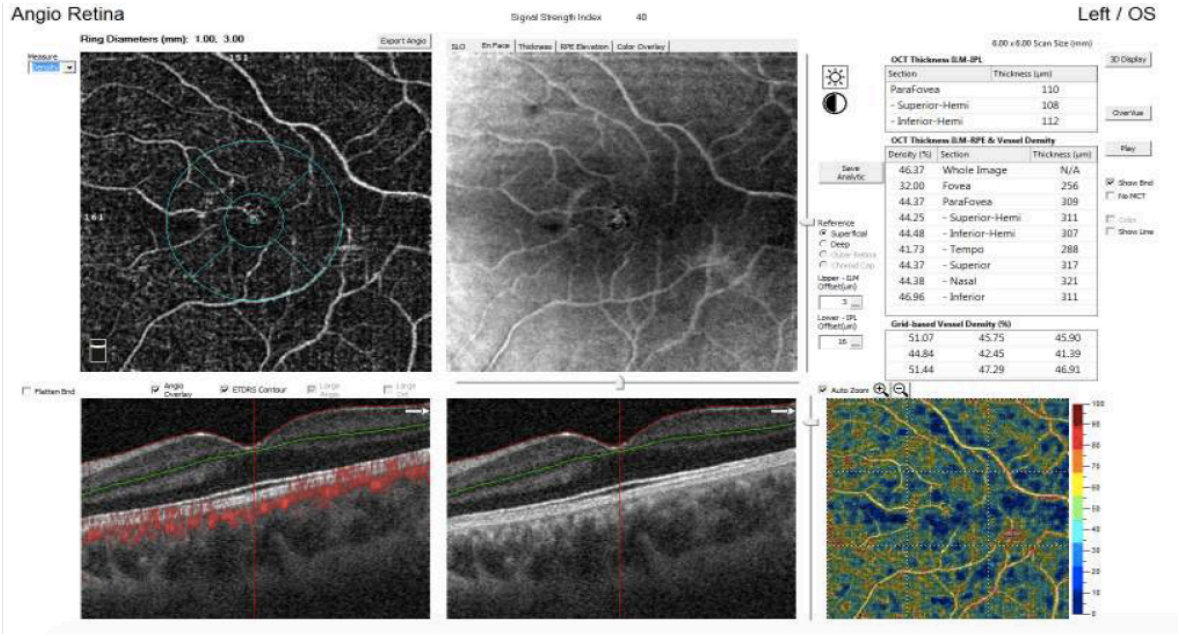

Figure 2. A 3x3 mm square image, centered on the fovea, is acquired. The central area was delineated by a grid consisting of two concentric circles with 1 and 3 mm radius, and a right angled cross at 45° and 135° to the horizontal. Vessel density assessment, along with segmentation, is automatically computed by the device and displayed for the whole image and the grid-based segments.

Vascular Flow

Mean vascular flow was automatically determined using a circle with 1.5 mm radius centered on the fovea **(Figure 3)**.

Mean vascular flow values for the baseline images and the post-operative serial evaluations are displayed in **Table 3**.

Table 3.

% (p)	Baseline	Week 1	Month 1
	35.42 ± 11.86	36.16 ± 11.25 (0.537)	35.54 ± 11.90 (0.669)

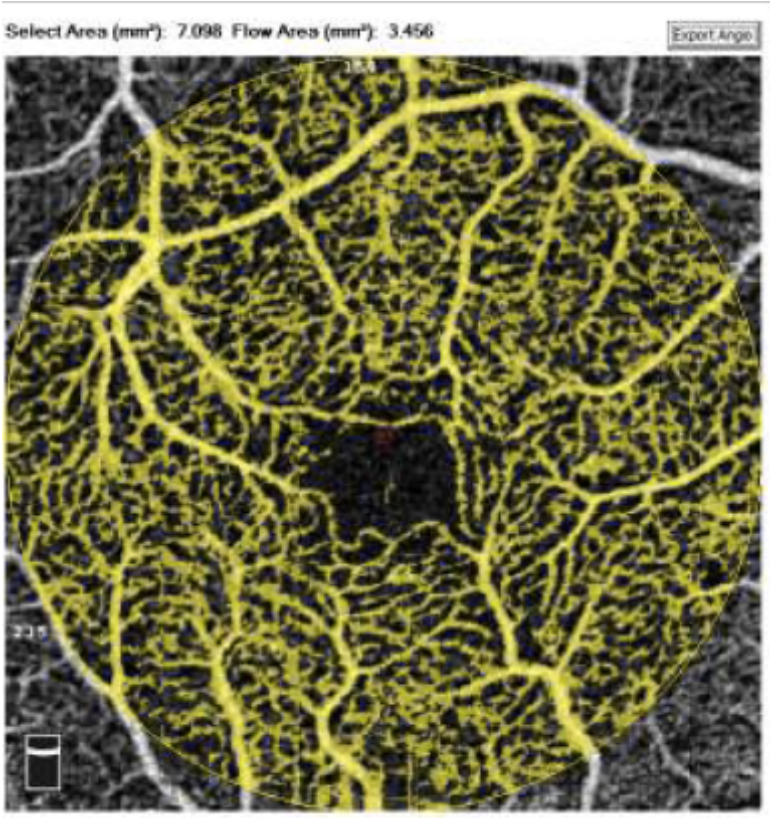

Figure 3. Example of flow area acquisition by the OCT-A device

Microperimetry

Microperimetry was performed by a single examiner (MS). The examination was conducted in a darkened room. A 1° circle was used as the fixation target. After a 30-second fixation test, all patients underwent brief training at the beginning of microperimetry allowing familiarization and practice with correct operation of the response trigger and the stimulus target. This was followed immediately by the microperimetry test. For the test stimulus, the color was white, the size was Goldmann III (26 minutes' arc or 0.4°), and the duration was 200 ms. A 45-loci grid covering the central 8° pattern was used. We used a 4-to-2 staircase strategy, to reduce testing time and possible fatigue.

Of the 10 patients enrolled on the study, 6 did not attend at least one of the scheduled microperimetry exams, rendering the comparison between baseline exam and post-operative

exam impossible. Two other subjects were excluded due to poor fixation and exam reliability, leaving only two patients included in the microperimetry assessment. On both cases there was no obvious overall difference between pre and post-operative microperimetry. The pre and post-operative mean sensitivity was 14.1 dB and 15.0 dB for patient 1, and 10.9 dB and 10.3 dB for patient 2, respectively. The pre and post-operative mean retinal defect was -5.9 and-5.0 for patient 1, and -9.0 and -9.4 for patient 2, respectively.

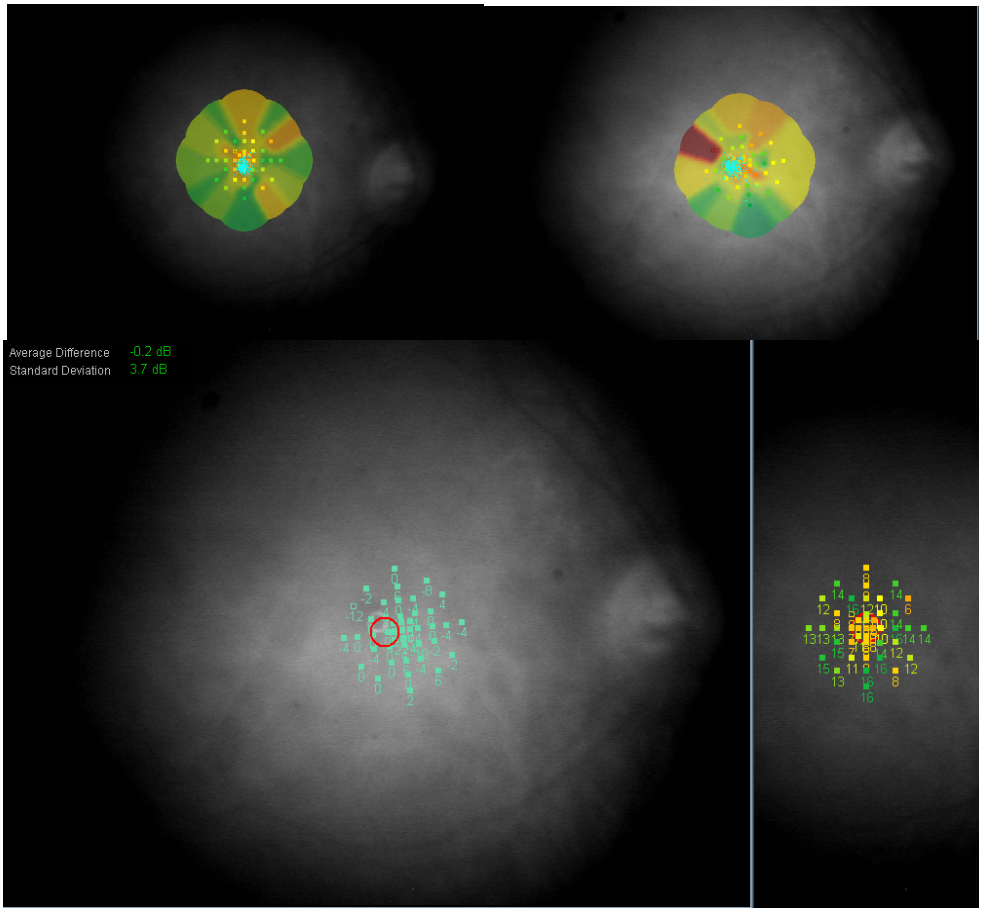

Figure 4. Example of patient 1. Interpolated test results for both pre-operative (A) and post-operative (B) microperimetry. A differential map between both exams was constructed (C), displaying an average difference of -0.2 dB (± 3.7).

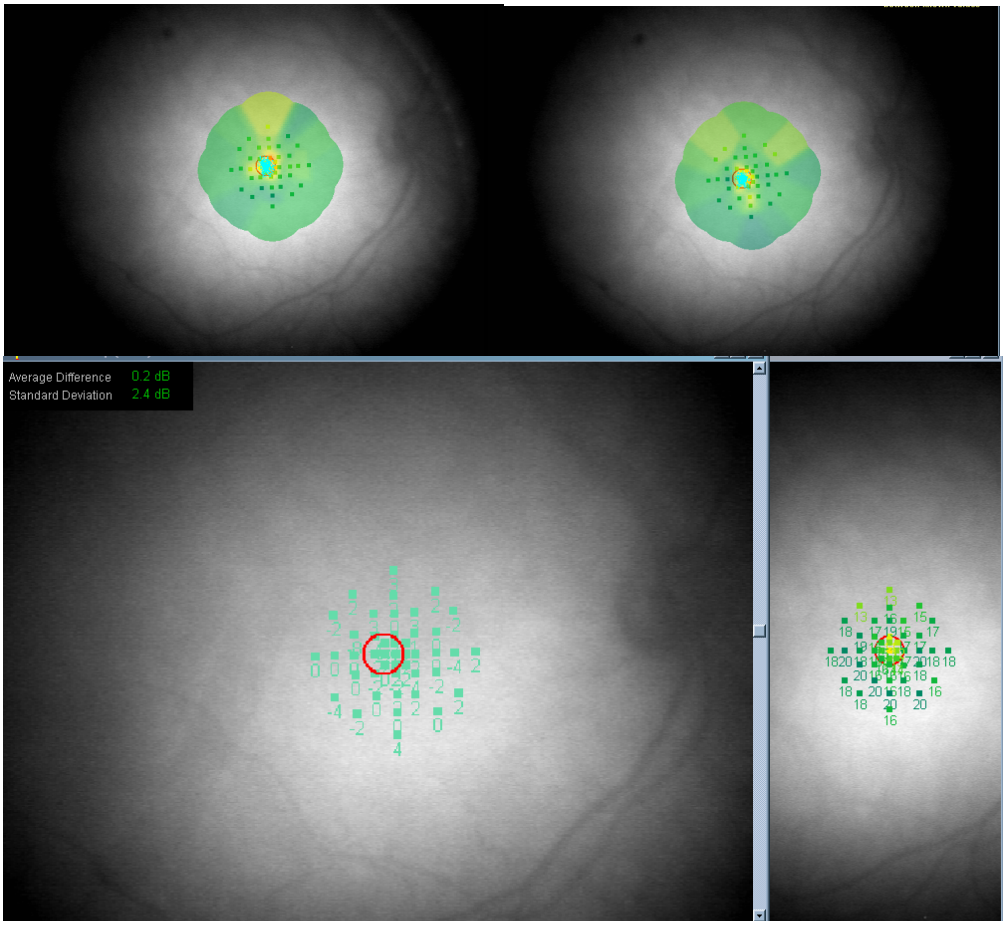

Figure 5. Example of patient 2. Interpolated test results for both pre-operative (A) and post-operative (B) microperimetry. A differential map between both exams was constructed (C), displaying an average difference of -0.2 dB (± 3.7).

DISCUSSION

Our exploratory study did not identify evidence of UVA induced retinal phototoxicity resulting from ACXL treatments, as observed by our morphologic and functional assessment of treated retinas in the immediate post-operatory period.

Keratoconus and Riboflavin-induced ultraviolet-light ACXL have received a significant amount of attention in recent years.[14] Previous studies have demonstrated the safety and efficacy of this technique for the prevention and progression of Keratoconus.[1516] Although this technique is used in the EU for almost a decade, it's implementation in the US

only took place in the last year, 2016, with the Food and Drug Administration (FDA) approbation and it's expected to become an increasingly common surgical procedure.

According to previous studies[17] it's known that UV light can damage the cornea, the lens and the retina. The ability of light and radiation to enact damage on the neurosensory retina and underlying structures - because it's the main agent used in ACXL treatment – motivated us to do a multimodal assessment of functional and structural retinal changes in patients undergoing ACXL. It is important to notice that this type of photon induced injury can happen even at light levels below the maximal permissible exposure defined by current safety standards, and has been reported with numerous common every-day procedures in Ophthamology.[6] Also, human eyes have an additional risk for retinal damage resulting from UV light during the first decades of life (<30 years), precisely when keratoconus is more incident[17].

The clinical aspects of macular phototoxicity have been described before and include a very faint foveal yellow spot on ophthalmoscopy and patient's complaints of a central scotoma.[18] Both structural and functional changes associated with photic maculopathy seem to naturally resolve shortly after surgery, making it difficult to diagnose and document. In the particular case of ACXL, patients are expected to experience some level of transient vision loss after treatment, due to corneal haze.[19] This effect makes it difficult for patients to notice blurred vision due to photic maculopathy, and for clinicians to detect and diagnose it, hence our particular interest in performing this study. In some cases, a macular dysfunction not visible in ophthalmoscopy may coexist and the low visual acuity could be due not only to the corneal abnormality but also to photoreceptor dysfunction.

The hallmarks of retinal photochemical damage on SD-OCT have been published before[18] and consist of a square-shaped hyporeflective space(s) in the outer retina ("partial

thickness hole"), without inner retinal cystic changes, as seen on the B-scan images. *En-face* OCT images aiming for the outer retina layers should show a discontinuity on the foveal zone, surrounded by a hyperreflective ring. All images on our patients were consistently reviewed with these signs in mind and no suggestive alterations were found. Also, the graders noted no other changes deemed significant, including other changes inconsistent with expected alterations due to photic damage.

Given the recent advances in OCT technology, we chose to include an additional assessment of the retinal structure of our patients. OCT-A is a recent and emerging technology that has great potential for use in the clinical setting. It has been proved to be a useful imaging modality for the evaluation of common ophthalmologic retinal diseases such as AMD, diabetic retinopathy, artery and vein occlusions, and glaucoma[20]. OCT-A shows the vascular structure of the retina *in* vivo without contrast agent. This technique precisely demonstrates the intravascular flow without the use of a dye. While this warrants a good visualization of the vessels, it does entail newer methods of imaging interpretation.[21,22] Known mechanisms of light damage to the retina include class I damage[23], involving the photoreceptor photopigments, and class II damage[24], causing particular damage to the RPE and relatively sparing the photoreceptors. None of the classical studies on photon-related injury to the retina have looked into vascular damage. However, photochemical damage is enacted through the creation of reactive oxygen species, a known key-factor in numerous vascular changes, from endothelial damage to angiogenesis stimulation.[25] One of the advantages of OCT-A, due to its fastness and simplicity, is the ability to perform multiple serial examinations. We speculated whether the ability to perform serial microvasculature assessment of the macula could uncover sub-clinical vascular changes due to photic damage never before reported. Noticeably, to the best of our knowledge, this is the first study to

evaluate the vascular macular structure in patients with keratoconus after ACXL surgery, using OCT-A.

This study used a commercially available OCT-A system and integrated and automated algorithms to examine macular vascular density and vascular flow area in patients post-ACXL treatment. We analysed the whole image and we proceeded to the 8 sub-regional areas evaluation.

Allied to OCT-A technology, we performed a microperimetric evaluation of our patients. This technique is the measurement of the patient's capability to perceive light originated in different positions across the field of view. In other words, it is the measurement of sensivity to light across the central retina. Depending on the retinal values of responsiveness, we can create map's of sensivity, allowing us to conclude if there were or not retinal alterations. As explained in previous sections, it allows the examiner to view the fundus on a screen while the images are made in real time by an infrared (IR) fundus camera.

The baseline vessel density of the whole image was 49.08%. Values for 1 week (48.66% - p=0.5) and 1 month (48.00% - p=0.5) were very similar, apparently showing little evidence that the retinal vessel architecture has changed.

Looking into the vessel density around the foveal area - the vessel density raised from 32.77% in the baseline, to 34.50% (p-0.23) the week after and 35.81% (p-0.5) the month after. No significant change was noted, again implying no evidence of vascular alterations.

Two of the sub-regional areas analysed – Inferior and Superior hemifield – had a decrease in the mean vessel density in both observations, 1 week after and 1 month.

The Parafoveolar area had a vessel density of 49.38%, raising in the first week to 50.03% (p-0.89), and decreasing the month after to 46.08% (p-0.225). All the other sub-regional areas – Superior, Inferior, Nasal and Temporal hemifields – had the same pattern

observed in the latter: a mean vessel density value that raised the first week after the surgical procedure, decreasing then to values under the baseline. However, regardless of absolute values measured, none of the changes observed were deemed statistically significant, implying no consistent change occurred in the vascular pattern of the central retina of our patients.

Our paper also looked into vascular flow, as measured by OCT-A. Mean vascular flow values are shown in Table3. The baseline value was 35.42 ± 11.86. Once again, considering the values after one week (36.16 ± 11.25 (0.537)) and one month (35.54 ± 11.90 (0.669)), no statistically significant changes were noted.

All the information we obtained from the OCT-A images is in concordance with normal OCT-A values for vessel densities previously published.[20] Also, the design of our study, where we have baseline values obtained before exposure to our presumed causative agent and strict time frames of observation for expected transient risk periods, provide us with a self-controlled design where each possible case could act as its own control. There was no statistically significant difference between the baseline values, 1-week follow-up and 1 month-follow-up in both exams - mean vessel density and vascular flow – which allows us to assume that the UVA radiation used in ACXL leads to no evidence of OCT-A visible vascular alterations and/or retinal vascular flow.

Two microperimetric evaluations were made – baseline exam and post-operative exam – in order to evaluate potential changes. Analysing the values obtained, there seems to be no obvious overall difference between pre and post-operative microperimetry, in agreement with the relative structural stability observed in the OCT-A analysis. Displayed above are the microperimetric maps – Figure 4 and Figure 5 – presenting both interpolated maps concerning the pre-op and the post-op exam, as well as a differential map constructed specifically for

change analysis. Subjective comparison of interpolated maps shows no generalized depression of foveal sensitivity, an interpretation sustained by the differential map. The average difference was ±0.2 dB in all performed exams. Unfortunately, there was a significant level. Regrettably, there was a high level of attrition concerning the completion of the functional assessment arm of the trial. Only 20% of the enrolled patients managed to successfully perform all the predefined exams which could potentially hinder our ability to extrapolate the results.

Although we strongly believe our results strengthen the body of evidence concerning ACXL safety, our study is not without limitations. It is limited in terms of patient population and has a short follow-up time. Consistent series of photic maculopathy are exceedingly rare for most ophthalmic procedures and, to our knowledge, completely inexistent when it comes to ACXL. The absence of a reliable prevalence figure makes it impossible to calculate an appropriate sample size, meaning our study may be underpowered for its goals. This is a limitation we cannot escape but our goal was to thoroughly assess possible retinal changes, albeit subclinical ones, and for that our sample seems valid. Also, descriptions of photic maculopathy in the literature describe it as appearing acutely after light injury and spontaneously resolving after some weeks, making the limited but strategic time points considered a reasonable approach. Some level of corneal haze is expected after ACXL and diminished corneal clarity could have the potential to hinder proper image acquisition by the OCT-A or microperimetry. However, none of the OCT-A images obtained were deemed non-gradeable or unreliable by the graders, and, with the exception of 2 exams, all patients managed to perform microperimetry appropriately. Therefore, we feel that anterior segment clarity was not an issue affecting the validity of our results.

CONCLUSION

In conclusion, our study suggests that there are no functional and structural retinal changes in patients undergoing ACXL treatment.

Further studies of ACXL with more patients and longer follow-up time are needed, particularly to inform guidelines to help ophthalmologists decide where, when, and what techniques are best suited to individual patients.

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