Early findings in a prospective randomised study on three cross-linking treatment protocols: interruption of the iontophoresis treatment protocol

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ABSTRACT

Purpose  To present the outcome of the interrupted iontophoresis-assisted treatment arm in an ongoing randomised clinical trial (NCT04427956).

Methods  A randomised clinical study of corneal cross-linking (CXL) using continuous UV-A irradiation at a rate of 9 mW/cm² and three different types of riboflavin and riboflavin delivery mode: (1) iso-osmolar dextran-based riboflavin (epithelium-off), (2) hypo-osmolar dextran-free riboflavin (epithelium-off) and (3) iontophoresis-assisted delivery of riboflavin (epithelium-on) for the treatment of progressive keratoconus. Inclusion criteria were an increase in the maximum keratometry value (Kmax) of 1.0 dioptre over 12 months or 0.5 dioptre over 6 months. The primary outcome in evaluating treatment efficacy was Kmax. Recently presented stratified detection limits were used post hoc to confirm the enrolment of patients with truly progressive keratoconus and in the assessment of the need for re-CXL.

Results  Thirteen patients had been randomised to iontophoresis-assisted CXL when the treatment arm was interrupted; two patients dropped out. Of the remaining 11 patients, 7 were deemed as having truly progressive disease according to the more recent stratified detection limits. The disease continued to progress in three patients according to the original definition (increase in Kmax ≥ 1 D), necessitating re-CXL with epithelium-off CXL. This progression was confirmed by post hoc analysis using the stratified detection limits for progression.

Conclusions  The iontophoresis-assisted CXL protocol failed to halt further disease progression in 27% of the patients. The failure rate increased to 38% when considering only the patients deemed to have truly progressive disease using the stratified detection limits.

INTRODUCTION

Corneal cross-linking (CXL) is performed to halt the progression of keratoconus disease. Preclinical studies have shown an increase in the biomechanical stiffness of the cross-linked cornea, and clinical studies have shown the efficacy of CXL in halting progressive keratoconus, thus reducing the need for corneal transplantation. However, evidence of the efficacy of CXL in halting keratoconus disease progression has also been questioned.

Cochrane reviews have suggested low evidence for the efficacy of CXL in halting progressive keratoconus, partially due to a lack of randomised clinical trials (RCTs). In addition, Cochrane authors have highlighted the importance of the accurate diagnosis of progressive keratoconus to ensure that patients with true progressive keratoconus are enrolled in clinical investigations. Keratometric parameters such as the maximum keratometry value (Kmax) and the steepest central keratometry value (K2) are among the most frequently used parameters to diagnose progression, and it is thus important to have knowledge of the repeatability of these parameters in order to distinguish between measurement error and true progression, both in diagnosing progression and when assessing the tomographic parameters after cross-linking.

The purpose of our ongoing RCT (NCT04427956) is to evaluate the efficacy in halting keratoconus disease progression using a continuous 9 mW/cm² Ultraviolet A (UV-A) (365 nm) source in three different treatment...
arms based on the type of riboflavin and the modality of riboflavin delivery: (1) an epithelium-off technique using dextran-based iso-osmolar riboflavin; (2) an epithelium-off technique using dextran-free hypo-osmolar riboflavin and (3) an epithelium-on technique using iontophoresis-assisted delivery of riboflavin.

The induction of corneal cross-links is an oxygen-dependent process, and increasing the irradiance will thus lead to the more rapid depletion of oxygen, resulting in a reduction in the number of cross-links, and consequently lower biomechanical stiffening. A 30 min of irradiation at a rate of 3 mW/cm² has been shown to be efficacious in inducing corneal stiffening; however, in this study, we chose a continuous irradiation rate of 9 mW/cm² for 10 min. Although this induces less stiffening than 30 min of irradiation at 3 mW/cm², it has been shown to have long-term efficacy in halting disease progression, and is less time-consuming in clinical practice. Furthermore, the shorter irradiation time reduces the risk of excessive thinning of the cornea during CXL. This means that more patients can be safely treated with CXL.

Dextran-based riboflavin is the original form of riboflavin used in the Dresden Protocol, it is the most frequently used type of riboflavin in clinical trials and was therefore included in this study. However, due to an oncotic effect of this form of riboflavin in association with evaporation of the stromal water from the de-epithelialised cornea, the corneal thickness can be reduced to below the safe limit, thus exposing the endothelial cells to excessive radiation. Therefore, we used hypo-osmolar riboflavin in the second treatment arm, as this has been suggested to cause less reduction in corneal thickness, thus rendering more patients eligible for safe CXL. However, both these protocols require epithelial debridement in order to soak the cornea, as the riboflavin molecule is too large to pass through the intact epithelium. Avoiding epithelial debridement could be advantageous in terms of reducing the risk of post-CXL keratitis and pain. In addition, this may allow for safe treatment of thinner corneas as there is less evaporation from an intact epithelium. An iontophoresis-assisted (epithelium-on) treatment arm was therefore included in the study. This technique allows the transepithelial passage of the negatively charged riboflavin molecule by an electromotive force. The stromal concentration of riboflavin obtained is lower than in epithelium-off protocols, but higher than in an epithelium-on protocol without iontophoresis.

Preliminary analysis of our results showed that a significant proportion of the patients treated with the iontophoresis-assisted protocol continued to show disease progression, necessitating re-CXL with epithelium-off CXL. This is in contrast to the findings of previous RCTs on iontophoresis-assisted CXL, of sufficient efficacy in halting disease progression. However, considering the preclinical evidence of lower biomechanical stiffening after epithelium-on CXL and the reported insufficient efficacy in halting keratoconus disease progression in (non-iontophoretic) transepithelial CXL, we deemed it unethical to continue with this treatment arm, and this form of treatment was ceased.

SUBJECTS AND METHODS

Study design


Patient enrolment and randomisation

Patients with keratoconus fulfilling the inclusion criteria were enrolled consecutively from 2017. The inclusion criteria were progressive keratoconus defined as: an increase of 1.0 D in Kmax during the past 12 months or 0.5 D during the past 6 months, and a history of deteriorating visual acuity (perceived or objective). Patients with a history of ocular pathology and ocular surgery were excluded. Pregnant and breastfeeding women were also excluded. Only patients aged ≥18 years were recruited. Contact lens wear was discontinued at least 2 weeks before tomographic measurements were made.

Sealed envelopes were prepared by Clinical Studies Sweden, a national facility supported by the Swedish Research Council. An envelope was opened after the patient agreed to participate in the study. Only one eye per participating patient was included to avoid possible paired-organ bias.

Pretreatment assessment

The pre-CXL assessment consisted of measurements of uncorrected visual acuity (UCVA) and best spectacle-corrected visual acuity (BSCVA) performed by opticians with long experience of refraction in keratoconus. Measurements were performed with a corneal tomographer (Pentacam HR, Oculus, Germany) followed by full confocal scanning of the cornea, in addition to an automated endothelial cell count (Gofoscan 4, Nidek Technologies Srl, Italy). Furthermore, a slit lamp examination was performed.

CXL procedure

A drop of povidone iodine (Minims 5% eye-drops, Bausch+Lomb, Ireland) was instilled in the eye followed by local anaesthesia (Tetracaine 1% eye-drops, Bausch+Lomb, Ireland). An eyelid speculum was positioned, and the corneal surface was flushed with balanced salt solution (BSS). The iontophoresis equipment (Iontofor CXL, Sooft SpA, Italy) was applied to the cornea and riboflavin (Ricrolin+, Sooft SpA, Italy) was instilled in the applicator until it covered the metal grid. An electric current of 1 mA was applied for 5 min. After iontophoresis, the cornea was gently flushed with BSS and a binocular hand-held slit lamp was used to confirm visible stromal saturation of riboflavin. The cornea was then irradiated with UV-A (UV-X 2000, IROC, Switzerland) using an irradiation rate of 9 mW/cm² for 10 min (total fluence 5.4 J/cm²). At the end of the treatment, a drop of levofloxacin, 5 mg/mL (Oftaquix, Santen Oy, Finland).
was applied. After CXL, levofloxacin (5 mg/mL) was prescribed four times a day for 7 days as a prophylaxis to prevent infection. In addition, a lubricating carbomer (Oftagel, 2.5 mg/g, Santen Oy, Finland) was prescribed four times a day for 1 month for comfort.

Post-treatment assessment
The patients returned to the clinic for follow-up visits after 7 days, and after 1, 6, 12 and 24 months. The purpose of the first visit after 7 days was to confirm healing of the corneal epithelium and to check for signs of infection. No further measurements were performed at this visit. At the 1-month visit, measurements were made with an anterior optical coherence tomographer (OCT) (3D OCT-2000, Topcon Medical Systems, USA) to examine the demarcation line, which is considered to indicate the depth of the cross-linking effect.33 In addition, full confocal scanning was performed to assess the treatment depth, and an automated endothelial cell density measurement was performed. At the 6, 12 and 24 months follow-up visits, the UCV and BSCVA were assessed, in addition to measurements with the Pentacam HR and automated endothelial cell density measurements. Four replicate measurements were made with the Pentacam HR on each follow-up occasion. Patients were instructed to discontinue using contact lenses 2 weeks prior to the follow-up visits.

Post hoc assessment of progressive keratoconus
After this study was started, the frequently used 1.0 D increase in Kmax to define progressive keratoconus was questioned.11 34 35 In fact, a strong association has been demonstrated between the repeatability of measurements of Kmax and keratoconus disease severity, implying that stratified detection limits based on disease severity should be used.11 In addition, it has been reported that the use of a single measurement, or a mean of replicates, on each occasion based on interday assessments of the repeatability, further contributes to the correct diagnosis of progression.36 37 These detection limits are hereafter referred to as stratified detection limits. A post hoc analysis was performed using these stratified Kmax detection limits to assess whether patients with true progressive keratoconus had been enrolled in the study.

The repeatability of post-CXL measurements has only been evaluated in the assessment of treatment efficacy following CXL in a few studies,36 while the association between the repeatability and disease severity has not been evaluated. This increases the uncertainty in the assessment of the efficacy of CXL. Thus, several parameters were assessed to avoid the overdiagnosis of continued progression after iontophoresis-assisted CXL. According to the Global Consensus Report on keratoconus and ectatic diseases,39 an increased curvature of the anterior and posterior corneal surfaces is suggestive of disease progression, as is reduced corneal thickness. Stratified detection limits for the parameters used to measure these anatomical changes have been suggested,36 37 namely, the central steepest keratometry value (K2), Kmax and the A, B and C parameters of the Belin ABCD Progression Display. Therefore, enhanced detection limits for these parameters were analysed for all patients demonstrating signs of continued progression, that is, an increase of ≥1.0 D in Kmax at any of the follow-up visits.

Statistical analysis
This randomised study was designed as a non-inferior study with dextran-based iso-osmolar riboflavin as the reference protocol. A null difference between the reference protocol and the other two protocols was set at 1.0 D in Kmax, and an SD of 1.2 D was assumed (alpha=0.025; power=0.81), resulting in a sample size of 24 patients in each group. Allocation rate 1:1:1. Bonferroni correction was applied. A discontinuation rate of 10% was anticipated, giving a sample size of 27 patients in each group. SAS Enterprise Guide V.6.1 for Windows (SAS Institute) was used to calculate the sample size.

The primary outcome variable was Kmax, and an increase in Kmax≥1.0 D was defined as treatment failure. Secondary outcomes were the depth of the demarcation line, the endothelial cell density, BSCVA and the spherical equivalent (SE). Due to the interruption of the iontophoresis-assisted treatment arm, the outcome of this arm will be analysed separately, and not compared with those of the other treatment arms.

RESULTS
At the time when the iontophoresis-assisted treatment arm was interrupted (2021), 13 subjects had been recruited. One of these patients opted out before the first follow-up visit, and another patient was unable to participate in the investigation, leaving 11 patients. All patients participated in the 1-month follow-up visit, but anterior segment OCT measurements could not be performed on two patients due to technical problems. Four patients did not attend the 6-month follow-up. One patient did not attend the 12-month follow-up, and another patient had already had re-CXL due to continued progression; both of which were excluded. Eight patients have so far attended the 24-month follow-up, and three are scheduled for follow-up later this year (2023). Another two patients showed continued progression at the 24-month follow-up and underwent re-CXL.

The baseline characteristics of the participants are presented in online supplemental table 1. The mean age was 24.6 years (range 20–29 years), and there was a male preponderance (7 of 11 patients). The mean progression in terms of Kmax was 1.44 D (range 0.6–2.6 D). According to the stratified detection limits, 8 of the 11 patients were deemed as having truly progressive disease. Other authors have also suggested detection limits based on a mean of measurements. Brunner et al suggested that an increase of 1.55 D in Kmax is indicative of disease progression when using a mean of three measurements. However, the precision with which progressive keratoconus is diagnosed can be further improved by increasing

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patients 8 and 10 and are therefore not presented. The detection limits reported by Brunner suggested no progression (green). If considering the A and C parameters suggested significant progression (orange). In patient 4, K2, Kmax and the A, B and C parameters suggested significant progression (shaded red), and K2 suggested possible progression. Eight patients attended the 24-month follow-up visit (ΔK2 (D) ΔKmax (D) ΔA (mm) ΔB (mm) ΔC (µm)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Follow-up visit</th>
<th>ΔK2 (D)</th>
<th>ΔKmax (D)</th>
<th>ΔA (mm)</th>
<th>ΔB (mm)</th>
<th>ΔC (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>24 months</td>
<td>+0.7</td>
<td>+1.6</td>
<td>-0.18</td>
<td>-0.25</td>
<td>-18</td>
</tr>
<tr>
<td>4</td>
<td>24 months</td>
<td>+2.1</td>
<td>+3.2</td>
<td>-0.14</td>
<td>-0.3</td>
<td>-17</td>
</tr>
<tr>
<td>5</td>
<td>6 months</td>
<td>+1.3</td>
<td>+1.3</td>
<td>0.04</td>
<td>-0.1</td>
<td>-3</td>
</tr>
</tbody>
</table>

ΔK2: difference in the central steepest keratometry reading from baseline, ΔKmax: difference in the maximum keratometry reading from baseline, ΔA, ΔB, ΔC: difference in the magnitude from baseline of the A, B and C parameters in the Belin ABCD Progression Display. Colour coding: green (no progression), orange (possible progression) and red (significant progression).

the number of replicate measurements (in this case four) and by considering the disease severity. Thus, a detection limit at 0.44 D of increase in Kmax was used for patients with Kmax<49 D and a detection limit at 1.08 was used for patients with Kmax≥49 D. These detection limits are in accordance with findings from previous investigations. The results of the follow-up visits at 1, 6, 12 and 24 months are presented in online supplemental table 2). Anterior segment OCT measurements were performed in nine of the eleven patients at the 1 month visit. Of these, the demarcation line was only visible in one patient. All patients attended the 12 month follow-up, at which time one patient had undergone re-CXL due to suspected progression. Eight patients attended the 24-month follow-up, and three are scheduled for follow-up later this year. Two patients were deemed to have progressive disease, and underwent re-CXL, thus a total of three patients underwent re-CXL. No adverse events occurred.

The results of the post hoc analysis of continued progressive keratoconus after iontophoresis-assisted CXL are presented in table 1. The three patients who showed an increase in Kmax of ≥1.0 D and consequently underwent re-CXL (denoted patients 3, 4 and 5), were re-evaluated using the stratified detection limits with regard to K2, Kmax and the A, B and C parameters from the Belin ABCD Progression Display. This post hoc analysis was performed to rule out the possibility that these patients underwent re-CXL unnecessarily because of overdiagnosis due to measurement error. In patient 3, Kmax and the A, B and C parameters suggested significant progression (shaded red), and K2 suggested possible progression (orange). In patient 4, K2, Kmax and the A and C parameters suggested significant progression and the B parameter suggested possible progression. In patient 5, K2, Kmax and the B parameter suggested significant progression, while the A and C parameters suggested no progression (green). If considering the detection limits reported by Brunner et al then patients 3 and 4 demonstrated significant progression in Kmax (detection limit at 1.55 D) and if considering K2 (detection limit at 0.75 D) then patients 4 and 5 demonstrated significant progression.

The results of anterior segment OCT 1 month after iontophoresis-assisted CXL for the patients are presented in online supplemental figures 1–11). Anterior segment OCT was not performed at the 1-month follow-up in patients 8 and 10 and are therefore not presented. The demarcation line was only visible in patient 11 (online supplemental figure 11).

DISCUSSION
Iontophoresis-assisted CXL has potential advantages in terms of time-efficient soaking of the cornea with riboflavin and preserving the epithelium intact, which could reduce pain and increase the safety of CXL. However, an intact epithelium is also disadvantageous as cross-linking is an oxygen-dependent process and an intact epithelium thus acts as a barrier to oxygen diffusion. In addition, the naturally high oxygen demand of the epithelium further reduces the oxygen availability. The rapid depletion of oxygen that occurs in epithelium-on CXL interrupts the cross-linking process, resulting in lower biomechanical stiffening compared with epithelium-off CXL.

The results presented here suggest that iontophoresis-assisted CXL is not sufficiently efficacious in halting the progression of keratoconus. In fact, 3 of the 11 patients (27%) showed continued progression, necessitating re-CXL. This increased to 38% when considering only the patients deemed to have truly progressive disease according to the stratified detection limits. This is in contrast to the results reported from two previous RCTs on iontophoresis-assisted CXL. In the first of these studies, the same equipment was used for the iontophoresis-assisted delivery of riboflavin and a similar UV-A irradiation rate of 10 mW/cm² for 9 min (total fluence 5.4 J/cm²). None of the participating patients (n=22) showed an increase in Kmax of ≥1.0 D after 1 year, however, two patients showed an increase of ≥1 D at the 24-month follow-up, although they were deemed not to require re-CXL. In the second study, iontophoresis-assisted delivery of riboflavin was administered for 10 min instead of 5 min, and the UV-A irradiation rate was 3 mW/cm² (total fluence 5.6 J/cm²). Only 1 of 76 patients was deemed to require re-CXL at the 24-month follow-up.

One factor that could have affected the outcome in the current study and in the two previous studies is age. Lower age is a well-known risk factor for progression. The mean age of the participants in this study was lower: 28.4±2.5 years in the previous RCTs. There is no specific age at which a patient is more prone to progression, but given the lower age in this study it is possible that the patients were more prone to progression.
Another factor that could contribute to the differences between the results of these RCTs is the way in which progressive keratoconus is diagnosed. Traditionally, a 1.0 D increase in Kmax has been used to define progression and the need for re-CXL. However, since the start of this study, the need to stratify detection limits according to disease severity has been demonstrated for several parameters, including Kmax.11 This is important in order to avoid underdiagnosis of progression in patients with less advanced keratoconus, and overdiagnosis of progression in those with moderate to advanced keratoconus.11 The detection limits can be further optimised when based on interday measurements and adjusted accordingly to the use of a single measurement or a mean of replicates.36 37 In this study, an increase of Kmax ≥1.0 D over 1 year or ≥0.5 D over 6 months was used, which is suboptimal given the current knowledge. The post hoc evaluation of these patients using the stratified detection limits showed that three patients were erroneously enrolled, none of which later showed further progression. In one of the previous RCTs,27 an increase of ≥1.0 D in Kmax was used as an enrolment criterion based on measurements with a combined Placido disk topographer and an anterior segment OCT (Visante, Carl Zeiss Meditec, Dublin, California, USA). In the other RCT,27 an increase in the steepest central keratometry value of ≥1.0 D or ≥0.5 D in spherical equivalent refraction measured with an autokerato-refractometer (NIDEK ARK 1000 OPD, NIDEK, Japan) was used. No studies have been carried out on the repeatability of measurements using these instruments in a keratoconus population, and no post hoc analysis of the patients in these RCTs could therefore be performed. However, the repeatability of measurements made with similar instruments namely Placido disk topography and anterior segment OCT and autokerato-refractometer, has been evaluated in patients with keratoconus, showing the need for stratified detection limits when diagnosing progressive keratoconus.11 33 It would, therefore, have been interesting to know whether the enrolment of the patients in the previous two RCTs had been affected by measurement error associated with disease severity.

It is equally important to consider the repeatability of the measurements used to assess treatment efficacy and the need for re-CXL, as both underestimation and overestimation of the treatment efficacy, and thus the need for re-CXL, could occur. Therefore, it was considered important to thoroughly evaluate the patients who needed re-CXL by post hoc analysis using the stratified detection limits for progression. As no investigations could be found on the repeatability of post-CXL measurements, similar to pre-CXL measurements, we applied the stratified detection limits based on measurements before CXL. Haze could affect the post-CXL measurements47; however, as this was not a common feature after iontophoresis-assisted CXL, we deemed it reasonable to use these detection limits. The post hoc assessment showed that there was true progression in the three patients who underwent re-CXL after initial iontophoresis-assisted CXL.

A third and fourth factor that could explain the differences between the outcome of this study and one of the previous studies27 is the length of the iontophoresis procedure and the irradiation rate. A longer iontophoresis-assisted delivery of riboflavin increases the stromal concentration of riboflavin, although not reaching the levels in epithelium-off CXL.25 26 In addition, a lower UV-A irradiation rate depletes the stromal oxygen at a slower rate,12 resulting in more induced cross-links and higher biomechanical stiffening, which has been reported in iontophoresis-assisted CXL.29 Therefore, those patients may have been subjected to a higher cross-linking effect than those in this study. One aspect that could support this hypothesis is the demarcation line. The demarcation line, considered to indicate the depth of the cross-linking effect,33 was only visible in one of the patients in this study, similar to findings in another RCT of transepithelial CXL.30 However, in the previous RCT with longer iontophoresis and lower irradiance,27 the demarcation line was visible in 45% of the patients, which could suggest a higher cross-linking effect. However, the demarcation line was visible in 96% of the patients and deeper in the reference cohort (epithelium-off, 3 mW/cm²). In fact, this is in accordance with a previous study26 suggesting that even if the UV-A irradiance rate is reduced to 1.5 mW/cm² (total fluence 5.4 J/cm²) in iontophoresis-assisted CXL, the efficacy is not as high as in epithelium-off CXL using UV-A at 3 mW/cm² (total fluence 5.4 J/cm²).

In conclusion, although iontophoresis-assisted CXL has a potential advantage in leaving the epithelium intact, we found that it failed to halt the progression of keratoconus disease in a significant proportion of the patients when using a 9 mW/cm² UV-A source. The likely explanation of this is the low stromal oxygen availability due to the intact epithelium, which arrests the induction of cross-links, resulting in lower biomechanical stiffening. We, therefore, concluded that this protocol is not suitable for halting keratoconus disease progression. Possible means of improving the efficacy of the iontophoresis-assisted protocol include a longer irradiation time, the addition of oxygen during treatment, or pulsed UV-A irradiation.48 We also concluded that the way in which progressive keratoconus is diagnosed, and the way in which treatment efficacy is evaluated, significantly affect the interpretation of the outcome. These aspects should be considered in future clinical investigations of CXL.

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Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The study is being conducted at the Department of Ophthalmology at Skåne University Hospital, Lund, Sweden, according to the tenets of the Declaration of Helsinki. All participants were given written information on the study, and written
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consent was obtained. The Regional Ethics Committee in Lund, Sweden, approved the study (No. 2015/373).

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