Progression of Keratoconus in Patients While Awaiting Corneal Cross-linking: A Prospective Clinical Study

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ABSTRACT

PURPOSE: To assess topographical changes in patients with keratoconus while awaiting corneal cross-linking (CXL) treatment.

METHODS: In this prospective, double-center, observational clinical study, patients with keratoconus were enrolled. Progression was defined as a change in the curvature within the cone area of at least 1.00 diopter (D) on tangential map and a thinning of 20 µm at the thinnest point after measurements taken at least 3 months apart. Morphological parameters were assessed at baseline (day of listing for CXL) and on the day of CXL treatment, including slit-lamp biomicroscopy, keratometry (maximum, minimum, and mean), and thinnest corneal thickness using corneal tomography (Pentacam; Oculus Optikgeräte GmbH, Wetzlar, Germany).

RESULTS: One hundred four eyes of 104 patients were included. The waiting time was 84.8 ± 62.9 days. Twenty-five percent of patients showed evidence of progression while waiting for treatment. Patients who progressed while waiting for treatment were younger (22.2 ± 6.79 years) compared to those who did not show evidence of progression (25.4 ± 5.62 years) (P = .02). Stratification by age groups showed a significant worsening of maximum keratometry of 1.18 ± 1.37 D in patients younger than 18 years compared to those 18 to 26 years of age and those older than 26 years (P = .002 and .042, respectively). The multivariate model confirmed that the progression steepening of the maximum keratometry while waiting for treatment was associated with age (P = .028).

CONCLUSIONS: The results suggest that stratification of waiting time according to the patient’s age is required to reduce the risk of further progression of keratoconus.

ferred for CXL at either The Royal Liverpool University Hospital, United Kingdom (64 patients), or The Eye Center, Humanitas Clinical and Research Center, Rozzano, Milan, Italy (40 patients), between September 2016 and March 2017. The study received institutional review board approval from both centers and was conducted according to the tenets of the Declaration of Helsinki, as revised in 2000.

The inclusion criteria were patients with keratoconus who had been referred for CXL. The patients were referred for documented progression of keratoconus. Progression was defined as a change in the curvature within the cone area of at least 1.00 diopter (D) on tangential map and a thinning of 20 µm in minimum corneal thickness when measured at least 3 months apart. Exclusion criteria were a history of herpetic keratitis, dry eye, severe corneal infection, concomitant ocular or systemic autoimmune disease, diagnosed pregnancy or breastfeeding, and a minimum corneal thickness of less than 400 microns.

The following parameters were assessed at baseline (day of listing for CXL) and on the day of CXL treatment: slit-lamp biomicroscopy, keratometry (maximum [Kmax], minimum, and mean), and thinnest corneal thickness using one scan of corneal tomography (Pentacam; Oculus Optikgeräte GmbH, Wetzlar, Germany). The documentation of the progression and all preoperative and postoperative morphological tests were performed in an identical manner in the two centers.

**Statistical Analysis**

Statistical analysis was performed using SPSS statistical software (version 20.0; IBM Corporation, Armonk, NY). Data are described as mean ± standard deviation. Data were analyzed and stratified by age according to a previous report. The Student’s t, analysis of variance, and post hoc tests were applied to assess the significance of differences between data. A P value of less than .05 was considered significant. A multivariate model was used with progression (yes/no) as the dependent variable against known risk factors, including waiting time, age, atopy, non-white European ethnicity, and advanced disease.

**RESULTS**

One hundred four eyes of 104 patients were prospectively evaluated. Seventy-two (69%) patients were male. The mean age was 25.2 ± 6.9 years (range: 14 to 50 years). Fifty-six (53%) patients were classified as atopic because they had a history of allergic eye disease, asthma, eczema, or hay fever. The overall waiting time was 84.8 ± 62.9 days.

Twenty-five percent of patients showed evidence of progression (ie, a change in maximum corneal curvature [Kmax] within the cone area of at least 1.00 D on tangential map) while waiting for treatment (Table 1). Patients who progressed while waiting for treatment were younger (22.2 ± 6.79 years) compared to those who did not show evidence of progression (25.4 ± 5.62 years) (P = .01).

To further investigate the significant difference in age between patients who had and had not progressed while waiting for treatment, patients were separated into three groups: younger than 18 years (28 patients), 18 to 26 years (40 patients), and older than 26 years (44 patients) (Table 2). Although there was a trend toward longer waiting times between groups, there was no significant difference in waiting times (P = .06) or distribution of patients with atopy within the groups (percentages of atopic patients were 47%, 60%, and 51% in patients younger than 18 years, 18 to 26 years, and older than 26 years, respectively).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Progressed</th>
<th>Not Progressed</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waiting time (days)</td>
<td>67.73 ± 34.89</td>
<td>90.7 ± 69.60</td>
<td>.10</td>
</tr>
<tr>
<td>Age (y)</td>
<td>22.2 ± 6.79 (14 to 37)</td>
<td>25.4 ± 5.62 (14 to 39)</td>
<td>.01</td>
</tr>
<tr>
<td>Ratio (M:F)</td>
<td>18:8</td>
<td>52:23</td>
<td>.58</td>
</tr>
<tr>
<td>Atopy (yes:no)</td>
<td>13:13</td>
<td>42:33</td>
<td>.38</td>
</tr>
<tr>
<td>Topographic indices at listing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kmax (D)</td>
<td>50.50 ± 6.00</td>
<td>49.40 ± 4.96</td>
<td>.33</td>
</tr>
<tr>
<td>Kmin (D)</td>
<td>45.80 ± 4.19</td>
<td>45.20 ± 3.75</td>
<td>.49</td>
</tr>
<tr>
<td>Kmean (D)</td>
<td>46.60 ± 2.91</td>
<td>46.80 ± 3.89</td>
<td>.80</td>
</tr>
<tr>
<td>ThCT (μm)</td>
<td>447.6 ± 63.25</td>
<td>462.3 ± 53.79</td>
<td>.25</td>
</tr>
</tbody>
</table>

Kmax = maximum keratometry; D = diopters; Kmin = minimum keratometry; Kmean = mean keratometry; ThCT = corneal thinnest point

*Values are presented as mean ± standard deviation unless otherwise noted.*
26 years, respectively. However, there was a significant worsening of Kmax during the waiting time in patients younger than 18 years. That is, Kmax increased by 1.18 ± 1.37 D in patients younger than 18 years compared to 0.085 ± 0.88 D in patients 18 to 26 years (P = .002) and 0.41 ± 1.24 D in patients older than 26 years (P = .042) (Figure 1). In a multivariate model that considered the Kmax difference with waiting time, age, and atopy, there was a significant association between the change in Kmax and age (P = .028). Any correlation was highlighted by a multivariate model that used progression (yes/no) as the dependent variable against known risk factors, including waiting time, age, atopy, non-white European ethnicity, and advanced disease (P = .10).

**DISCUSSION**

CXL is becoming an established procedure to reduce the progression of keratoconus.10-12 Currently, although there are no clear international guidelines for the exact cut-off to indicate clear progression, an increase of curvature supported by another criterion is usually required. This has been defined as an increase of Kmax11 or astigmatism,13 a subjective loss of vision,14 or a corneal thinning of more than 20 µm in minimum corneal thickness.12,15

When a patient with keratoconus has shown evidence of progression, CXL is indicated,16 regardless of the age of the patient.17 We found that younger patients, particularly those younger than 18 years, had a significantly greater incidence of progression during the waiting period, with a change in Kmax that was greater than the standard cut-off to indicate CXL. This was despite a trend of older patients waiting for a longer period of time. This is important because the change in Kmax in younger patients was more than 1.00 D and may have affected vision with irreversible loss of sight because CXL is not always able to regress the progression of the disease.18

![Figure 1. Scatterplot showing the changes in maximum keratometry (Kmax) versus the age of the patient.](image)

Although atopy was not found to be a significant factor for progression during the waiting period, this result should be taken with caution considering the relatively small number of patients. Additionally, the definition of atopy may need to be restricted to evidence of atopic conjunctivitis and whether the atopy is active or controlled.

However, even if the accepted cut-off for progression of keratoconus is 1.00 D, this could be mistaken for an error of the measurement in some cases. As a matter of fact, it is known that the 95% interobserver limit of agreement for Kmax is 1.01 D for Pentacam-derived Krumeich stage 1 or 2, but can go up to 3.86 D for stages higher than stage 2. Of concern, even if the mean waiting list time was just longer than 2 months, this was sufficient time for there to have been an increase in Kmax of more than 1.00 D. This value, even if it might be incorrect for keratoconus with a stage higher than 2, should cause suspicion of progression inside the waiting list.19
There are a few studies in the literature that have shown an increased rate of progression in patients with pediatric and atopic keratoconus, but none of them evaluated the waiting list time. However, Chatzis et al. proposed that waiting for documentation of progression should not be mandatory and CXL in children and adolescents should be performed as soon as the diagnosis has been made.

Our results confirm the previous literature findings indicating that pediatric patients tend to have a faster progression of the disease compared to the other age groups. Of concern, even if the mean waiting list time was just longer than 2 months, this was sufficient time for there to have been an increase in Kmax of more than 1.00 D. This outcome highlights the need to create different waiting list times according to age and possibly other identifiable risk factors. Although speculative, based on our results, if we consider a linear progression of the patients during the waiting period, patients younger than 18 years would worsen by 0.50 D in 4 to 6 weeks, which is half of the cut-off to consider that a patient has progressed. For this reason, we suggest a waiting time of no longer than 12 weeks for patients older than 18 years and less than 6 weeks for those younger than 18 years.

AUTHOR CONTRIBUTIONS
Study concept and design (VR); data collection (RV, EMA, NH, PR, PV); analysis and interpretation of data (VR, SBK); writing the manuscript (VR, RV, EMA, NH); critical revision of the manuscript (PR, PV, SBK); statistical expertise (VR, SBK); supervision (PV, SBK)

REFERENCES