CXL: Clinical results

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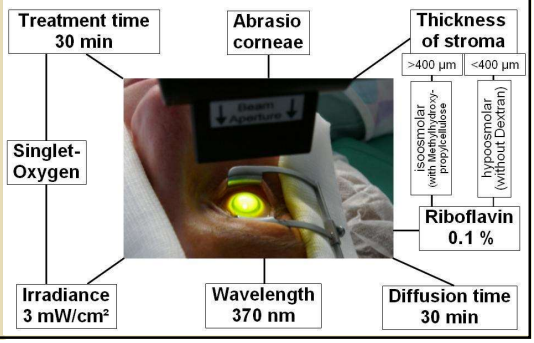
Chairman: Prof. L.E. Pillunat, MD

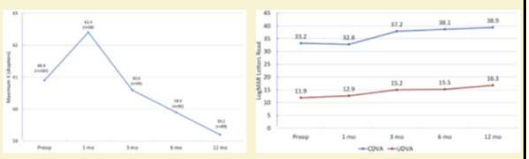
Epi-off

Standard Treatment Parameters



United States Multicenter Clinical Trial of Corneal Collagen Crosslinking for Keratoconus Treatment

Peter S. Hersh, MD,[1] R. Doyle Stulting, MD, PhD,[2] David Muller, PhD,[3] Daniel S. Durrie, MD,[4] Rajesh K. Rajpal, MD,[5,6] on behalf of the United States Crosslinking Study Group*



Conclusions: Corneal collagen crosslinking was effective in improving the maximum keratometry value, CDVA, and UCVA in eyes with progressive keratoconus 1 year after treatment, with an excellent safety profile.

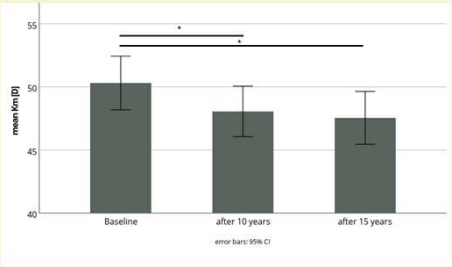
Ophthalmology 2017; 124: 1259-1270

CXL: 15-year results

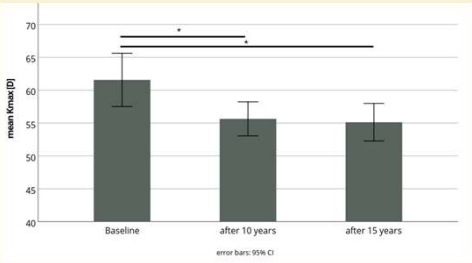
- 47 eyes of 36 patients
- CXL between 1998 and 2006
- F/U after 10 and 15 years
- CXL perfomed according Dresden Protocol
- linear mixed model used to evaluate the data taking into account the inter-eye correlation

Raiskup F, Herber R, Lenk J et al. Corneal crosslinking with riboflavin and UVA light in progressive keratoconus: fifteen-year results. Am J Ophthalmol. 2023; 250: 95-102

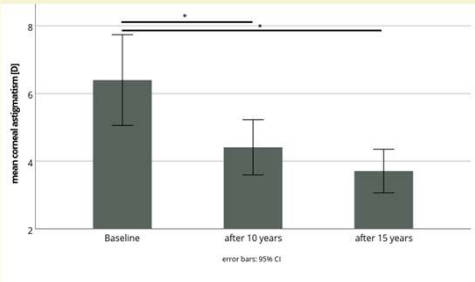
K_{mean}



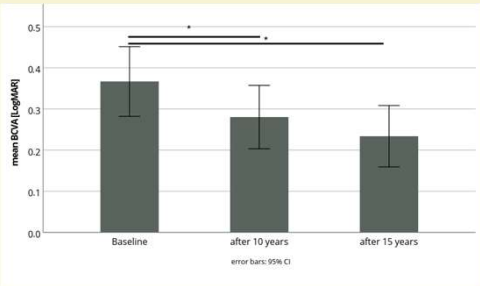
K_{apex}



Astigmatism



Visual acuity



CXL: 15-year results

- haze in 16/47 eyes (34%)
- re-CXL (13 %) in mean period after 1. CXL 7.8 ± 4.3 y.

Re-CXL: risk factors

- high preoperative Kmax
- neurodermatitis combined with other atopic disease

Lenk J, Herber R, Oswald Ch. et al. Risk factors for progression of keratoconus and failure rate after corneal cross-linking. J Refract Suef. 2021; 37: 816-823

Corneal Collagen Cross-Linking With Riboflavin and Ultraviolet A Light for Pediatric Keratoconus: Ten-Year Results

Cosimo Mazzotta, MD, PhD,† Claudio Traversi, MD,* Stefano Baiocchi, MD, PhD,* Simone Bagaglia, MD,* Orsola Caporossi, MD,‡ Antonio Villano, MD,§ and Aldo Caporossi, MD§*

- 62 eyes of 47 patients
- mean age: 14±2,4 y. (8-18y.)
- 80% male
- KC stability in nearly 80%
- progression rate 20% (15 y. and younger)

Cornea 2018; 37: 560-566

Effect of CXL vs. standard care on keratoconus progression in young patients

- progression in the CXL group occured in 7% compared to 43% in the standard care group
- CXL should be considered as a first-line treatment in progressive disease

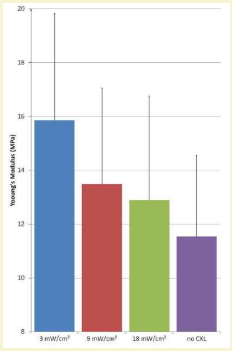
Larkin DFP, Chowdhury K, Burr JM et al. Effect of corneal cross-linking versus standard care on keratoconus progression in young patients. The KERALINK randomized controlled trial. Ophthalmology 2021; 128: 1516-1526

Accelerated CXL

- shortens the illumination time by increasing the illumination intensity (Bunsen-Roscoe law of reciprocity)
- reduces the overall treatment time

Accelerated CXL

- The **biomechanical effect of CXL decreased significantly when using high irradiance/short irradiation time settings.** Intrastromal oxygen diffusion capacity and increased oxygen consumption associated with higher irradiances may be a limiting factor leading to reduced treatment efficiency.



Hammer A, Richoz O, Mosquera SA et al. Corneal biomechanical properties at different corneal CXL irradiances. IOVS 2014; 55: 2881-2884

Accelerated Corneal Collagen Cross-Linking Protocols for Progressive Keratoconus: Systematic Review and Meta-analysis

Mohammad Karam, MBChB, Abdulmalik Alsaif, MBChB,† Ahmed Aldubaikhi, MBBS,‡§ Meshaal Aljebreen, MBBS,¶ Rand Alazzaz, MBBS,¶ Nathlia Alkhowailer, MD,‖ Tariq Almudhaiyan, MD,**†† and Faisal Aljassar, FRCS**

Purpose: The aim of this study was to compare the outcomes of 18 mW/cm² (5 minutes) versus 9 mW/cm² (10 minutes) accelerated corneal collagen cross-linking protocols in patients with progressive keratoconus.

Methods: A systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines, and electronic information was searched to identify studies comparing the outcomes of 5- versus 10-minute protocols in patients with progressive keratoconus. Mean changes in uncorrected visual acuity, best-corrected visual acuity, cylinder (diopters), thinnest corneal thickness, corneal keratometry values (K1 and K2), corneal high-order aberration (HOA), spherical aberration, coma, and trefoil were the primary outcome measures. Secondary outcome measures included the mean change in central corneal thickness and postoperative complications. Random effects modeling was used for the analysis.

Conclusions: The 10-minute protocol had better K1, K2, and HOA outcomes than the 5-minute protocol, but no statistically significant differences in the other outcomes.

Cornea 2023; 42: 252-260

Comparison of standard and accelerated corneal cross-linking for the treatment of keratoconus: a meta-analysis

Mehdi Shajari,[1] Carolin M. Kolb,[1] Bishr Agha,[1] Gernot Steinwender,[2] Michael Müller,[1] Eva Herrmann,[3] Ingo Schmack,[1] Wolfgang J. Mayer[4] and Thomas Kohnen[1]

- 22 studies with 1158 eyes
- „…less corneal thinning favours A-CXL, whereas the deeper demarcation line and greater changes in minimum keratometric values in C-CXL may indicate a higher efficacy…“
- both procedures provide successful results in the strengthening of corneal tissue

Acta Ophthalmol. 2019; 97: e22-e35

Analysis of the outcomes of three different cross-linking protocols for treatment of paediatric keratoconus: A multicentre randomized controlled trial

Mohammed Iqbal[1] | Ahmed Gad[1] | Ahmed Kotb[2] | Mahmoud Abdelhalim[3]

Purpose: To analyse long-term outcomes of standard cross-linking (SCXL), accelerated cross-linking (ACXL) and transepithelial cross-linking (TCXL) in the treatment of progressive paediatric keratoconus regarding stability, safety and efficacy.

Conclusion: SCXL and ACXL were comparable in halting keratoconus progression and achieved good stability and safety; however, SCXL was more efficient than ACXL as it yielded greater significant postoperative mean visual, refractive and keratometric improvements achieving smoother corneal remodelling. Both SCXL and ACXL were much superior to TCXL. SCXL is the best CXL treatment option for paediatric keratoconus while ACXL is a good and effective alternative.

Acta Ophthalmol. 2023; 00: 1-12

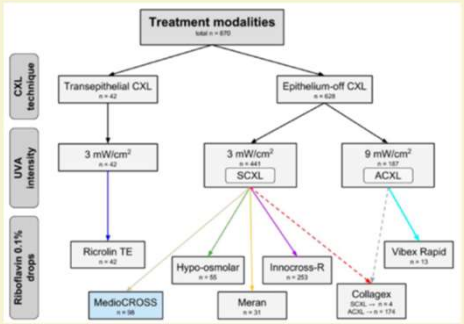
Complications of A-CXL

- delayed epithelial healing - 1,8% (in patients with vernal keratoconjunctivitis)
- haze formation in early postoperative period - 9,1%
- sterile infiltrates - 1,2%
- infectious keratitis - 0,5%
- treatment failure - 4,2%
- loss of 2 or more Snellen lines - 2,4%
- scar - 1,3%

Cakmak S, Sucu ME, Yildrim Y et al. Complications of accelerated corneal collagen cross-linking: review of 2025 eyes. Int Ophthalmol 2020; 40:3269-3277

The Independent Effect of Various Cross-Linking Treatment Modalities on Treatment Effectiveness in Keratoconus

Daniel A. Godefrooij, MD, PhD, Suzanna L. Rooké, MD, Nienke Soeters, PhD, and Robert P.L. Wisse, MD, PhD



Cornea 2020;39:63–70

The Independent Effect of Various Cross-Linking Treatment Modalities on Treatment Effectiveness in Keratoconus

Daniel A. Godefrooij, MD, PhD, Suzanna L. Rooké, MD, Nienke Soeters, PhD, and Robert P.L. Wisse, MD, PhD

- TE-CXL and accelerated protocol appeared to be associated with lower efficacy in halting keratoconus progression
- one-third of the cases treated with TE-CXL required retreatment

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Transepithelial versus Epithelium-off Corneal Collagen Cross-linking for Corneal Ectasia

A Systematic Review and Meta-analysis

Siddharth Nath, MD, PhD,[1] Carl Shen, MD,[2] Alex Koziarz, MSc,[3] Laura Banfield, MLIS,[4] Behnam Nowroozi-Kia, MD, MPH,[5] Mark A. Fava, MD,[2] William G. Hodge, MD, PhD[2–7]

Results: Twelve studies totaling 966 eyes were eligible. A significant difference was found between transepithelial and epithelium-off cross-linking groups in the change in K_{max} at 12 months (MD, 0.75; 95% CI, 0.23–1.28; $P = 0.004$; primary outcome) and at longest follow-up (MD, 1.20; 95% CI, 0.62–1.77; $P < 0.001$; secondary outcome) after treatment. No significant difference was found between the 2 groups when examining uncorrected distance visual acuity (MD, 0.04; 95% CI, −0.06 to 0.14; $P = 0.386$) or corrected distance visual acuity (MD, 0.01; 95% CI, −0.06 to 0.09; $P = 0.732$). Transepithelial cross-linking was associated with significantly fewer complications than the epithelium-off approach (RR, 0.22; 95% CI, 0.06–0.79; $P = 0.020$), although it was associated with an increased rate of disease progression at 12 months after treatment (RR, 4.49; 95% CI, 1.24–16.25; $P = 0.022$). The required information size was met for our primary outcome and trial sequential analysis supported the conventional meta-analysis. The quality of evidence was rated as moderate using the Grading of Recommendations Assessment, Development, and Evaluation methodology.

Discussion: The efficacy of transepithelial cross-linking remains inferior to the epithelium-off approach, although it is significantly safer. *Ophthalmology 2021;128:1150-1160 © 2020 by the American Academy of Ophthalmology*

Iontophoresis

- 586 eyes from three randomised controlled trials and seven comparative studies were analyzed
- no differences were found in the change in UDVA/CDVA, K_{max}, TCT, HOA, DL depth in both CXL protocols
- there was a significant reduction in complications following I-CXL

Wan KH, Ip ChKY, Kua WN et al. Transepithelial corneal collagen cross-linking using iontophoresis versus the Dresden protocol in progressive keratoconus: A meta-analysis. Clin Experiment Ophthalmol. 2021; 49: 228-241

Does Corneal Collagen Cross-linking Reduce the Need for Keratoplasties in Patients With Keratoconus?

Gunhild Falleth Sandvik, MPhil, Andreas Thorsrud, MD,* Marianne Råen, MPhil,* Atle E. Østern, MD, PhD,* Marit Sæthre, MD, PhD,* and Liv Drolsum, MD, PhD*†*

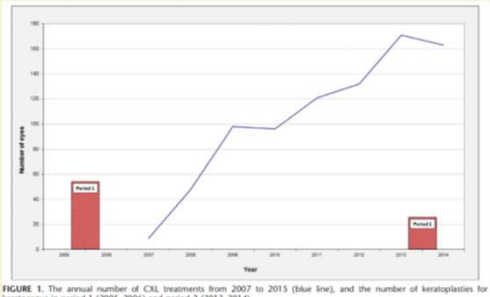
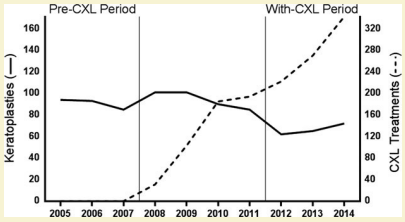


FIGURE 1. The annual number of CXL treatments from 2007 to 2015 (blue line), and the number of keratoplasties for keratoconus in period 1 (2005–2006) and period 2 (2013–2014).

Cornea 2015; 34(9): 991-995

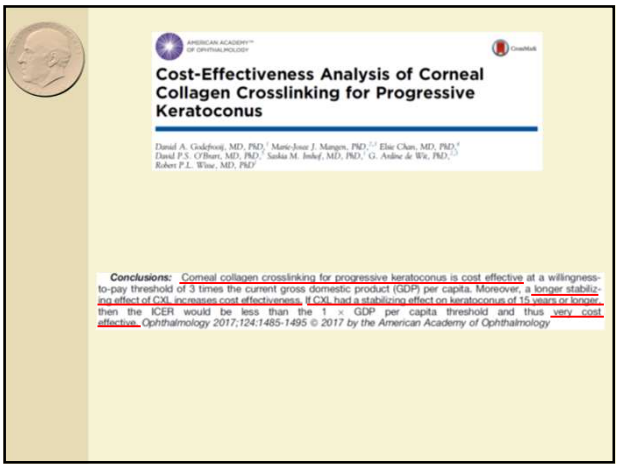
Nationwide reduction in the number of corneal transplantations for keratoconus following the implementation of cross-linking

Daniel A. Godefrooij, Renze Gans, Saskia M. Imhof and Robert P. L. Wisse



Results: Approximately 25% fewer corneal transplants were performed in the 3-year period following the introduction of CXL compared to the 3-year period prior to the introduction of CXL (201 versus 269 transplants, respectively; p = 0.005). Age, gender and visual acuity were similar between the patient groups in the two time periods. Trend analysis also demonstrated a significant decrease in the amount of corneal transplants (p = 0.001).

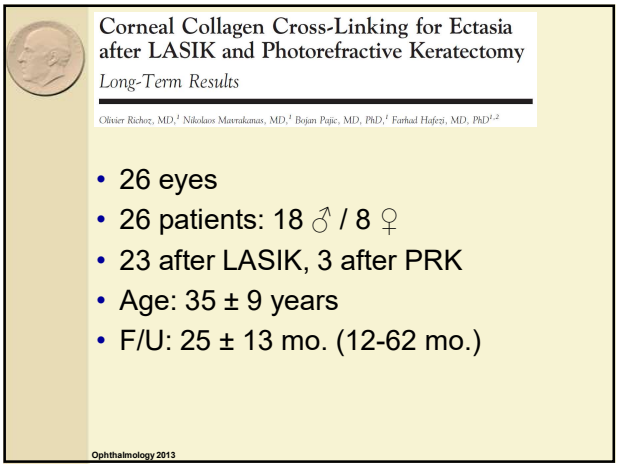
Acta Ophthalmol. 2016



Cost-Effectiveness Analysis of Corneal Collagen Crosslinking for Progressive Keratoconus

Daniel A. Godefrooij, MD, PhD,[1] Marie-Josee J. Mangen, PhD,[2,3] Elsie Chan, MD, PhD,[4] David P.S. O'Brart, MD, PhD,[5] Saskia M. Imhof, MD, PhD,[1] G. Ardine de Wit, PhD,[2,3] Robert P.L. Wisse, MD, PhD[1]

Conclusions: Corneal collagen crosslinking for progressive keratoconus is cost effective at a willingness-to-pay threshold of 3 times the current gross domestic product (GDP) per capita. Moreover, a longer stabilizing effect of CXL increases cost effectiveness. If CXL had a stabilizing effect on keratoconus of 15 years or longer, then the ICER would be less than the 1 × GDP per capita threshold and thus very cost effective. *Ophthalmology 2017;124:1485-1495 © 2017 by the American Academy of Ophthalmology*



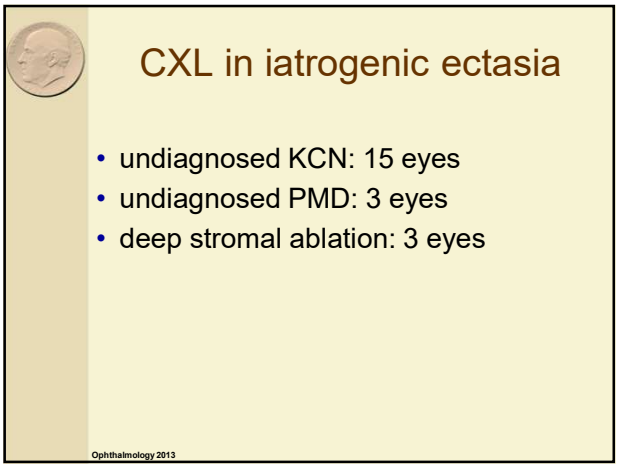
Corneal Collagen Cross-Linking for Ectasia after LASIK and Photorefractive Keratectomy

Long-Term Results

Olivier Richoz, MD,[1] Nikolaos Mavrakanas, MD,[1] Bojan Pajic, MD, PhD,[1] Farhad Hafezi, MD, PhD[1,2]

- 26 eyes
- 26 patients: 18 ♂ / 8 ♀
- 23 after LASIK, 3 after PRK
- Age: 35 ± 9 years
- F/U: 25 ± 13 mo. (12-62 mo.)

Ophthalmology 2013



CXL in iatrogenic ectasia

- undiagnosed KCN: 15 eyes
- undiagnosed PMD: 3 eyes
- deep stromal ablation: 3 eyes

Ophthalmology 2013

CXL in iatrogenic ectasia

- CDVA improved in 19 cases
- CDVA remained stable in 7 cases
- K_{max} improved in 19 cases
- K_{max} remained stable in 7 cases
- no serious complications reported postoperatively

Ophthalmology 2013

CXL in iatrogenic ectasia

- „…long-term stability without significant side effects…“
- „…accelerated CXL seems to be safe and effective in halting postoperative LASIK ectasia progression after 2 years…“

Yildirim A, Cakir H, Kara N. Corneal collagen crosslinking for ectasia after laser in situ keratomileusis: long-term results. JCRS 2014; 40: 1591-1596
Marino GK, Torricelli AA, Giacomin N et al. Accelerated corneal collagen cross-linking for postoperative LASIK Ectasia: two-year outcomes. JRS 2015; 31:380-384

Long term efficacy and stability of corneal collagen cross linking for post-LASIK ectasia: an average of 80mo follow-up

Walid Sharif[1,2], Zaid Rushdi Ali[2], Khaled Sharif[2]

- 17 eyes of 13 patients
- mean age: 31 y. (23 – 39y.)
- mean follow-up: 80,7±15 mo. (57-102mo.)
- UDVA remained stable or improved ≥1 Snellen lines in 88,2%
- CDVA remained stable or improved ≥1 Snellen lines in 76,5%
- significant decrease of Kmax

Int J Ophthalmol 2019; 12: 333-337

Corneal Cross-Linking for Keratoconus and Post-LASIK Ectasia and Failure Rate: A 3 Years Follow-Up Study

Wassef Chamboure [1], Lulwa El Zein [2], Mohamad Ali Younes [3], Mohamad Issa [4], Pramod Warhekar [3], Elias Chelala [5], Elias Jarade [3]

1. Ophthalmology, Beth Israel Deaconess Medical Center (BIDMC), Boston, USA 2. Pediatric Ophthalmology, Bascom Palmer Eye Institute, Miami, USA 3. Internal Medicine, Faculty of Medical Sciences - Lebanese University, Hadath, LBN 4. Ophthalmology, Hospital Foundation Adolphe De Rothschild, Paris, FRA 5. Ophthalmology, Medclinic City Hospital, Dubai, ARE 6. Ophthalmology, Saint Joseph University, Beirut, LBN 7. Ophthalmology, Beirut Eye & ENT Specialist Hospital, Beirut, LBN

Results

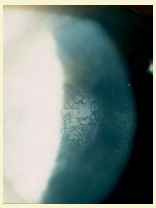
In KC, CDVA, spherical equivalence, sphere, cylinder, and mean K improved at three years post-CXL (p-value<0.05), but these values improved without reaching a statistical significance in ectasia(p-values <0.05). 12 of 54 eyes with ectasia (22.2%) and 4 of 111 eyes (3.6%) with KC had progression post CXL(p-value:0.0001). Ectasia patients diagnosed with progression were older at presentation (36.1 years) than non-progressive ectasia patients (31 years) (p-value 0.02) and also older than KC patients.

Conclusion

Eyes with post-LASIK ectasia seem to be less responsive to CXL than KC.

Cureus 2021; 13(11): e 19552

CXL in iatrogenic ectasia
Complication: epithelial ingrowth



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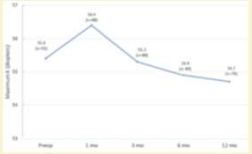
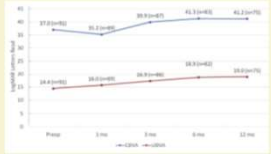
U.S. Multicenter Clinical Trial of Corneal Collagen Crosslinking for Treatment of Corneal Ectasia after Refractive Surgery

*Peter S. Hersh, MD,[1,2] R. Doyle Stulting, MD, PhD,[3] David Muller, PhD,[4] Daniel S. Durrie, MD,[5] Rajesh K. Rajpal, MD,[4,6] for the U.S. Crosslinking Study Group**





Conclusions: Corneal collagen crosslinking was effective in improving the maximum K value, CDVA, and UDVA in eyes with corneal ectasia 1 year after treatment, with an excellent safety profile. CXL is the first approved procedure to diminish progression of this ectatic corneal process. *Ophthalmology 2017;124:1475-1484 © 2017*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