



TITLE: Corneal Cross-linking with Riboflavin for Keratoconus: Update of Clinical and Cost-effectiveness

DATE: 24 November 2014

RESEARCH QUESTIONS

1. What is the clinical effectiveness of corneal collagen cross-linking for patients with keratoconus and other corneal thinning disorders?
2. What is the cost-effectiveness of corneal collagen cross-linking for patients with keratoconus and other corneal thinning disorders?

KEY FINDINGS

One systematic review and meta-analysis, one randomized controlled trial, and 10 non-randomized studies were identified regarding the clinical effectiveness of corneal collagen cross-linking for patients with keratoconus and other corneal thinning disorders. No relevant cost-effectiveness literature was identified.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 11), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and November 19, 2014. Internet links were provided, where available.

SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

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Table 1: Selection Criteria

| | |
|----------------------|---|
| Population | Patients with keratoconus and other corneal thinning disorders (e.g., keratectasia, pellucid marginal degeneration) |
| Intervention | Corneal collagen cross-linking with riboflavin and ultraviolet-A radiation |
| Comparator | Alternate treatments for keratoconus, e.g., contact lenses, corneal implants or other surgical interventions, placebo |
| Outcomes | Improved vision, improved corneal strength and/or stabilization, corneal thickness, corneal curvature, side effects, cost, cost-effectiveness |
| Study Designs | Health technology assessment reports, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations |

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines.

One systematic review and meta-analysis, one randomized controlled trial, and 10 non-randomized studies were identified regarding the clinical effectiveness of corneal collagen cross-linking for patients with keratoconus and other corneal thinning disorders. No relevant health technology assessment reports, economic evaluations, or evidence-based guidelines were identified.

Additional references of potential interest are provided in the appendix.

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

1. Chunyu T, Xiujun P, Zhengjun F, Xia Z, Feihu Z. Corneal collagen cross-linking in keratoconus: a systematic review and meta-analysis. *Sci Rep.* 2014;4:5652.
[PubMed: PM25007895](#)

Randomized Controlled Trials

2. Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. *Ophthalmology.* 2014 Apr;121(4):812-21.
[PubMed: PM24393351](#)

Non-Randomized Studies

3. Kanellopoulos AJ, Asimellis G. Epithelial remodeling after partial topography-guided normalization and high-fluence short-duration crosslinking (Athens protocol): results up to 1 year. *J Cataract Refract Surg.* 2014 Oct;40(10):1597-602.
[PubMed: PM25176050](#)

4. Padmanabhan P, Radhakrishnan A, Venkataraman AP, Gupta N, Srinivasan B. Corneal changes following collagen cross linking and simultaneous topography guided photoablation with collagen cross linking for keratoconus. Indian J Ophthalmol [Internet]. 2014 Feb [cited 2014 Nov 24];62(2):229-35. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4005242>
[PubMed: PM23619500](#)
5. Tomita M, Yoshida Y, Yamamoto Y, Mita M, Waring G. In vivo confocal laser microscopy of morphologic changes after simultaneous LASIK and accelerated collagen crosslinking for myopia: one-year results. J Cataract Refract Surg. 2014 Jun;40(6):981-90.
[PubMed: PM24857441](#)
6. Alessio G, L'Abbate M, Sborgia C, La Tegola MG. Photorefractive keratectomy followed by cross-linking versus cross-linking alone for management of progressive keratoconus: two-year follow-up. Am J Ophthalmol. 2013 Jan;155(1):54-65.
[PubMed: PM23022158](#)
7. Lamy R, Netto CF, Reis RG, Procopio B, Porco TC, Stewart JM, et al. Effects of corneal cross-linking on contrast sensitivity, visual acuity, and corneal topography in patients with keratoconus. Cornea. 2013 May;32(5):591-6.
[PubMed: PM23023410](#)
8. Poli M, Cornut PL, Balmitgere T, Aptel F, Janin H, Burillon C. Prospective study of corneal collagen cross-linking efficacy and tolerance in the treatment of keratoconus and corneal ectasia: 3-year results. Cornea. 2013 May;32(5):583-90.
[PubMed: PM23086357](#)
9. Rechichi M, Daya S, Scorcia V, Meduri A, Scorcia G. Epithelial-disruption collagen crosslinking for keratoconus: one-year results. J Cataract Refract Surg. 2013 Aug;39(8):1171-8.
[PubMed: PM23796620](#)
10. Salman AG. Transepithelial corneal collagen crosslinking for progressive keratoconus in a pediatric age group. J Cataract Refract Surg. 2013 Aug;39(8):1164-70.
[PubMed: PM23790531](#)
11. Toprak I, Yildirim C. Scheimpflug parameters after corneal collagen crosslinking for keratoconus. Eur J Ophthalmol. 2013 Jun 9;23(6):793-8.
[PubMed: PM23787458](#)
12. Viswanathan D, Males J. Prospective longitudinal study of corneal collagen cross-linking in progressive keratoconus. Clin Experiment Ophthalmol. 2013 Aug;41(6):531-6.
[PubMed: PM23145528](#)

Economic Evaluations

No literature identified.

Guidelines and Recommendations

No literature identified.

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APPENDIX – FURTHER INFORMATION:

Systematic Reviews and Meta-analyses - Unclear Comparator

13. Craig JA, Mahon J, Yellowlees A, Barata T, Glanville J, Arber M, et al. Epithelium-off photochemical corneal collagen cross-linkage using riboflavin And ultraviolet A for keratoconus and keratectasia: a systematic review and meta-analysis. *Ocul Surf.* 2014 Jul;12(3):202-14.
[PubMed: PM24999102](#)

Guidelines and Recommendations

14. Photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A for keratoconus and keratectasia [Internet]. London : National institute for health and Clinical Evidence; September 2013 [cited 2014 Nov 24] 11 p. (NICE interventional procedure guidance 466). Available from : <https://www.nice.org.uk/guidance/ipg466>
See: Recommendations, page 2.

Additional References

15. AHRQ Healthcare Horizon Scanning System Potential High-Impact Interventions Report - Priority Area 08: Functional Limitations and Disability [Internet]. Rockville (MD): Agency for Healthcare Research and Quality; June 2014. [cited 2014 Nov 24]. Available from: <http://effectivehealthcare.ahrq.gov/ehc/assets/File/Functional-Limitations-Horizon-Scan-High-Impact-1406.pdf>
See: Corneal Collagen Cross-Linking (VibeX/KXL System) for Treatment of Progressive Keratoconus, page 17.