MEDICINE & PUBLIC HEALTH
e-ISSN 2956-9443

2024, Vol. 2, No. 2
DOI: 10.48269/MandPH-AFMKU-24-2-002
Received: 2025-04-21
Accepted: 2025-06-11

REVIEW PAPER

Advancing Keratoconus Treatment. The Promise of Theranostic Technology

Anna Maria Roszkowska[1,2,D–F], *Marco Lombardo*[3,4,A,D]

[1] Department of Biomedical Sciences, University of Messina, Italy

[2] Clinic of Ophthalmology, Medical College, Andrzej Frycz Modrzewski Krakow University

[3] Vision Engineering Italy

[4] Studio Italiano di Oftalmologia

A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

Abstract

Background: Keratoconus (KC), a progressive ectatic disorder of the cornea, presents significant challenges in clinical management due to its unpredictable progression and individualized nature. Advances in treatment modalities, particularly corneal cross-linking (CXL), have revolutionized the ability to halt disease progression. Yet, a significant gap remains in achieving personalized, outcome-driven interventions.
Material and methods: Literature review.
Results: New personalized CXL approach based on theranostic biomarkers proved safe and effective in the treatment of KC and offers personalized approach to treat the disease.
Conclusions: Theranostics technology integrated with advanced UV-A device for CXL procedure permits to deliver the precise therapeutical dose of riboflavin and personalized UV-A light amount for the photo-activation in the cornea. This real-time monitoring of riboflavin concentration in the cornea during CXL procedure permits to obtain better predictability of the final outcome on personal basis.
Keywords: corneal cross-linking, keratoconus, theranostic

Introduction

Keratoconus (KC) is a corneal disease characterized by progressive ectasia with corneal thinning and steepening. It can cause a visual impairment that in severe forms, especially in young patients, requires corneal transplantation. Clinical signs of KC manifest frequently at puberty when the progression is more aggressive compared to adult onset, as the disease

✉ Anna Maria Roszkowska; email: aroszkowska@unime.it

usually halts in the fourth decade of life. Disease prevalence depends on the geographical location, reaching 5% in the Middle East [1–4].

Corneal cross-linking (CXL) based on riboflavin/UV-A interaction is a well-established procedure worldwide that induces corneal stiffening and is used to slow down or halt KC progression. Riboflavin exhibits photosensitizing properties in the presence of UV-A light and reacts with a wide range of electron-donating substrates through photochemical mechanisms. The main mechanism of the riboflavin/ UV-A CXL procedure relies on the direct interaction between riboflavin triplets and reactive groups of stromal proteins which induce the cross-linking of the proteins through radical reactions [5–7].

Several CXL protocols have been clinically validated for the treatment of keratoconus. They differ in the type and time of riboflavin application and UV-A irradiance treatment settings. The first CXL protocol, the so-called Dresden protocol, provides for the removal of the corneal epithelium and administration of a dextran-enriched riboflavin ophthalmic solution on to the corneal stroma for 30 min. Subsequently, the cornea is irradiated by a UV-A light device with 3 mW/cm power density for 30 min. to obtain a total delivered energy density of 5.4 J/cm^2. In the past decade, different UV-A treatment protocols have been developed and validated in the clinic [8–11]. At the same time, different riboflavin ophthalmic solutions have been used with their higher benefit/safety profile assessment based on pre-clinical and clinical evidence [12,13]. Nevertheless, the CXL treatment proved to be a valid therapy that reduced significantly the number of keratoplasties in patients with KC [8,14]. According to scientific evidence, the efficacy of the procedure shows a huge variation. CXL with epithelial removal is considered the most effective so far, but it represents the primary predisposing factor for major complications. In fact, adverse effects of the epithelium-off protocol include ocular pain, transient corneal oedema and corneal haze, and in some cases severe events, such as corneal infections, melting and corneal scarring with vision loss [15–17]. Several treatment protocols without epithelium removal, so called epithelium-on, have been developed in order to minimize these complications, although their clinical efficacy still remains an object of debate [9,18–21]. Nowadays, transepithelial CXL treatment protocol remains challenging since it is difficult to understand the real amount of the riboflavin penetrating into the corneal stroma through the intact epithelium.

Thus, it is evident that a precise knowledge of the principles of UV-A light/riboflavin interaction with the cornea could prove fundamental in improving the therapeutic management of keratoconus with CXL

[22]. Mathematical models and experimental studies have supported the hypothesis that the concentration of riboflavin in the cornea before UV-A light irradiation is the most important variable influencing the therapeutic effect of CXL treatment [22–23].

Recently, theranostic-guided corneal cross-linking using a theranostic UV-A medical device has been made available for treating keratoconus. Theranostic technology, a revolutionary approach combining therapy with diagnostic capabilities, is poised to address this gap by enabling precise, predictable, and personalized treatments for keratoconus.

What is Theranostic Technology?

Theranostics is an emerging and innovative therapeutic paradigm for precise and personalized medicine. Theranostics integrates therapeutic intervention with real-time diagnostics to optimize treatment strategies. Theranostic technology integrated with an advanced UV-A device for CXL enables the precise therapeutic dose of riboflavin and its UV-A light photo-activation to be customized to the individual cornea. The purpose of this real-time monitoring of corneal riboflavin concentration on a personal basis is to improve the predictability of clinical outcomes and to minimize risks of adverse events.

In the context of keratoconus, theranostic technology is embodied in a UV-A light device that utilizes feedback-driven algorithms to guide corneal cross-linking. This innovative system employs advanced imaging and predictive modelling to monitor corneal response to UV-A exposure during the procedure.

The theranostic UV device works by first capturing the corneal topography and wavefront aberrations in high resolution. These diagnostic measurements are used to model the biomechanical properties of the cornea and predict its response to UV-A irradiation. During treatment, the device continuously adjusts UV-A light delivery on the basis of real-time feedback, ensuring a precise reshaping of the cornea's curvature while minimizing collateral tissue damage. By tailoring the treatment parameters to the individual's unique corneal anatomy and biomechanical profile, theranostics not only enhances the safety and efficacy of the procedure but also allows clinical outcomes to be predicted with unparalleled accuracy (Figure 1).

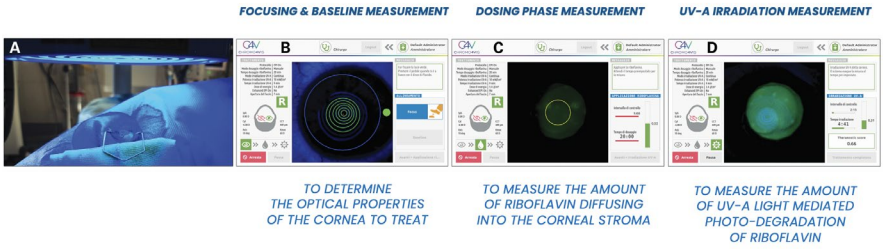

Figure 1. Theranostic device (A). Focusing and baseline measurement (B). Measure of riboflavin amount during soaking (C). Measurement of riboflavin amount during cross-linking process (D)

The ARGO Trial: Validating Precision in Predictive Keratoconus Treatment

The ARGO trial, a landmark study published in *Ophthalmology*, provides robust evidence supporting the efficacy and predictive capabilities of theranostic-guided corneal cross-linking. This multicentre, prospective clinical trial enrolled patients with progressive keratoconus to evaluate the technology's ability to achieve predictable and consistent treatment outcomes [24].

Key findings from the ARGO trial include:

1. Predictive Accuracy: The trial demonstrated a 91% accuracy rate in predicting the flattening of the maximum keratometry (Kmax) value at the 1-year follow-up. This level of precision highlights the reliability of the device's predictive algorithms in guiding treatment.
2. Treatment Precision: The theranostic-guided UV-A system achieved 95% precision in delivering the intended Kmax flattening, underscoring its ability to adhere to personalized treatment goals.
3. Clinical Outcomes: Patients experienced significant and consistent improvements in corneal curvature, with minimal adverse effects. The reduction in higher-order aberrations further contributed to enhanced visual quality.

These results mark a paradigm shift in keratoconus management, establishing theranostics as a cornerstone for precise and personalized interventions.

Expanding the Horizons: New Opportunities in Keratoconus Treatment

The success of theranostic-guided UV-A treatment opens up new avenues for advancing keratoconus care. Beyond its proven efficacy in halting disease progression, the technology paves the way for transformative applications:

1. Enhanced Early Diagnosis and Monitoring
   Theranostics enables the integration of diagnostic and therapeutic workflows, allowing clinicians to identify keratoconus at its earliest stages. Early detection, combined with predictive modelling, facilitates timely intervention to prevent significant visual deterioration.
2. Customizable Treatment Protocols
   By leveraging individualized corneal biomechanics and topography, theranostics allows for the development of customized treatment protocols. This adaptability ensures that patients with varying disease severities and anatomical variations receive optimal care.
3. Application in Other Corneal Disorders
   The principles of theranostics are not confined to keratoconus alone. The technology's potential extends to other corneal conditions, such as pellucid marginal degeneration and post-refractive surgery ectasia, where precise biomechanical modulation is critical.
4. Integration with Artificial Intelligence (AI)
   The future of theranostics lies in its synergy with AI-driven algorithms. Machine learning can enhance the predictive accuracy of theranostic devices by analyzing vast datasets of corneal response patterns. This integration will further refine treatment protocols and improve patient outcomes.
5. Development of Patterned UV-A Treatments
   Research is already underway to explore patterned theranostic-guided UV-A treatments. This approach aims to selectively target specific corneal regions for cross-linking, offering a more nuanced and effective solution for irregular astigmatism and advanced keratoconus cases.

Challenges and Future Directions

While theranostics represents a significant advancement in keratoconus treatment, challenges remain in its widespread adoption. The technology's complexity necessitates specialized training for clinicians, and its integration into clinical practice requires robust infrastructure and regulatory approvals. Additionally, cost considerations may pose barriers to accessibility, particularly in resource-limited settings.

Future research should focus on addressing these challenges through the development of cost-effective devices, streamlined training programs, and expanded clinical trials to validate the technology across diverse patient populations. Collaboration between industry leaders, academic institutions, and regulatory bodies will be essential to drive innovation and ensure equitable access to theranostic-guided treatments.

Conclusion

Theranostic technology heralds a new era in keratoconus management, offering a precise, predictive, and personalized approach to treatment. The validation provided by the ARGO trial underscores its potential to redefine clinical outcomes, enhancing both patient satisfaction and quality of life. As the field continues to evolve, theranostics is set to expand its impact, not only within ophthalmology but also as a model for integrating diagnostics and therapy across medical disciplines. By embracing this cutting-edge technology, clinicians and researchers have the opportunity to transform the standard of care for keratoconus and beyond.

Conflict of interest

Anna M Roszkowska no one, Marco Lombardo is co-inventor of the Patents IT102016000007349, EP3407920B1 and CN201680080266.9 for theranostic-guided corneal cross-linking.

References

1. Rabinowitz YS. Keratoconus. *Surv Ophthalmol*. 1998;42(4):297–319.
2. Gomes JAP, Rodrigues PF, Lamazales LL. Keratoconus epidemiology: A review. *Saudi J Ophthalmol*. 2022;36(1):3–6.
3. Godefrooij DA, de Wit GA, Uiterwaal CS, Imhof SM, Wisse RPL. Age-specific incidence and prevalence of keratoconus: a nationwide registration study. *Am J Ophthalmol*. 2017;175:169–172.
4. Kristianslund O, Hagem AM, Thorsrud A, Drolsum L. Prevalence and incidence of keratoconus in Norway: a nationwide register study. *Acta Ophthalmol*. 2021;99(5):e694–e699.
5. Zhang Y, Conrad AH, Conrad GW. Effects of ultraviolet-A and riboflavin on the interaction of collagen and proteoglycans during corneal cross-linking. *J Biol Chem*. 2011;286(15):13011–13022.
6. Sel S, Nass N, Pötzsch S, Trau S, Simm A, et al. UVA irradiation of riboflavin generates oxygen- dependent hydroxyl radicals. *Redox Rep*. 2014;19(2): 72–79.

7. Kamaev P, Friedman MD, Sherr E, Muller D. Photochemical kinetics of corneal cross-linking with riboflavin. *Invest Ophthalmol Vis Sci*. 2012;53(4):2360–2367.
8. Angelo L, Boptom AG, McGhee C, Ziaei M. Corneal Crosslinking: Present and Future. *Asia Pac J Ophthalmol*. 2022;11(5):441–452.
9. Nath S, Shen C, Koziarz A, Banfield L, Nowrouzi-Kia B, et al. Transepithelial versus epithelium-off corneal collagen cross-linking for corneal ectasia. *Ophthalmology*. 2021;128(8):1150–1160.
10. Hagem AM, Thorsrud A, Sabdvik GF, Drolsum L. Randomized study of collagen cross-linking with conven- tional versus accelerated UVA irradiation using riboflavin with hydroxypropyl methylcellulose: two-year results. *Cornea*. 2019;38(2):203–209.
11. Hashemi H, Ambrósio R Jr, Vinciguerra R, Vinciguerra P, Roberts CJ, et al. Two-year changes in corneal stiffness parameters after accelerated corneal cross-linking. *J Biomech*. 2019;93:209–212.
12. Lombardo M, Serrao S, Lombardo G, Schiano-Lomoriello D. Two-year outcomes of a randomized controlled trial of transepithelial corneal crosslinking with iontophoresis for keratoconus. *J Cataract Refract Surg*. 2019;45(7):992–1000.
13. Lombardo M, Micali N, Villari V, Serrao S, Pucci G, et al. Ultraviolet A: visible spectral absorbance of the human cornea after transepithelial soaking with dextran-enriched and dextran-free riboflavin 0.1% ophthalmic solutions. *J Cataract Refract Surg*. 2015;41(10):2283–2290.
14. Godefrooij DA, Gans R, Imhof SM, Wisse RPL. Nationwide reduction in the number of corneal transplantations for keratoconus following the implementation of cross-linking. *Acta Ophthalmol*. 2016;94(7):675–678.
15. Dhawan S, Rao K, Natrajan S. Complications of Corneal Collagen Cross-Linking. *J Ophthalmol*. 2011;2011:869015.
16. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. *J Cataract Refract Surg*. 2009;35(8):1358–1362.
17. Serrao S, Lombardo G, Lombardo M. Adverse events after riboflavin/UV-A corneal cross-linking: a literature review. *Int Ophthalmol*. 2022;42(1):337–348.
18. Wen D, Song B, Li Q, Tu R, Huang Y, et al. Comparison of epithelium-Off versus transepithelial corneal collagen cross-linking for keratoconus: a systematic review and meta-analysis. *Cornea*. 2018;37(8):1018–1024.
19. Ng SM, Ren M, Lindsley KB, Hawkins BS, Kuo IC. Transepithelial versus epithelium-off corneal crosslinking for progressive keratoconus. *Cochrane Database Syst Rev*. 2021;3(3):CD013512.
20. Zhang X, Zhao J, Li M, Tian M, Shen Y, Zhou X. Conventional and transepithelial corneal cross-linking for patients with keratoconus. *PLoS ONE*. 2018;13(4):e0195105.
21. D'Oria F, Palazón A, Alio JL. Corneal collagen cross-linking epithelium-on vs. epithelium-off: a systematic review and meta-analysis. *Eye Vis*. 2021;8(1):34.

22. Lombardo M, Pucci G, Barberi R, Lombardo G. Interaction of ultraviolet light with the cornea: clinical implications for corneal crosslinking. *J Cataract Refract Surg*. 2015;41(2):446–459.
23. Lombardo G, Micali NL, Villari V, Serrao S, Lombardo M. All-optical method to assess stromal concentration of riboflavin in conventional and accelerated UV-A irradiation of the human cornea. *Invest Opthalmol Vis Sci*. 2016;57(2):476–483.
24. Roszkowska AM, Scorcia V, Mencucci R, Giannaccare G, Lombardo G, et al. Assessment of the Predictive Ability of Theranostics for Corneal Cross-linking in Treating Keratoconus: A Randomized Clinical Trial. *Ophthalmology*. 2024;131(12):1403–1415.