ORIGINAL ARTICLE

Theranostic-guided Corneal Phototherapy for Precise and Predictive Treatment of Keratoconus and Ectatic Corneal Disorders: A Case Series

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Abstract

Aim and background: To report a case series of patients treated by theranostic-guided transepithelial corneal phototherapy for keratoconus and corneal ectasia.

Materials and methods: The clinical outcomes of three representative patients affected by keratoconus or iatrogenic corneal ectasia were treated with theranostic ultraviolet (UV) device (C4V CHROMO4VIS, Regensight srl). A 0.22% riboflavin ophthalmic solution (RitSight, Regensight srl) was applied before UV-A light phototherapy in all cases. The theranostic UV device integrates advanced molecular imaging diagnostic tools, including real-time analysis of imaging biomarkers, to treat and assess treatment response of the individual cornea, enabling predictive personalization of therapeutic outcomes.

Results: Patients underwent theranostic-guided transepithelial corneal phototherapy for keratoconus, either as primary treatment or as a retreatment following standard corneal cross-linking (CXL) failure, as well as for iatrogenic corneal ectasia. All patients showed significant improvements in visual acuity [by two or more early treatment diabetic retinopathy study (ETDRS) lines] and corneal topography (K_{max} flattened by ≥3.8 D) up to 2-year follow-up. Corneal total high-order aberrations significantly decreased in the same period in all cases.

Conclusion: Theranostic-guided transepithelial corneal phototherapy provides a safe and highly effective treatment for ectatic corneal disorders (ECDs). Its precise and predictive treatment approach, maintaining the corneal epithelium intact, enhances clinical outcomes while minimizing the risks of treatment failure and complications.

Clinical significance: Integrating theranostics technology into a UV device shows a promising advancement in the management of ECDs.

Key words: Case series, Corneal cross-linking, Riboflavin, Theranostics, Visual acuity.

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Introduction

Ectatic corneal disorders (ECDs) represent a significant challenge in ophthalmology due to their chronic, progressive degenerative course and the potential to substantially impair vision and decrease quality of life.[1] Traditional treatment approaches for halting disease progression of these conditions include riboflavin/UV-A corneal cross-linking (CXL), a technique aimed at stabilizing the corneal structure by inducing additional cross-link bonds among stromal proteins.[2] Although this conventional method has proven beneficial, there is still room for improvement, particularly in terms of predictable efficacy; meta-analyses have shown that CXL efficacy varies widely between studies, ranging from 10 to 90%, and these uncertainties in individual corneal responses may delay appropriate care by failing to detect treatment failure in time.[3,4]

Recently, theranostics has emerged as a promising technological advancement in the management of corneal disorders.[5] By combining molecular imaging diagnostic and therapeutic elements, theranostic-guided corneal phototherapy offers a novel, more personalized and precise targeted approach for treating ECD.[6–8] This technique utilizes UV-A light both for treatment and for generating molecular imaging biomarkers to precisely measure corneal riboflavin concentration, as well as to estimate improvements in corneal biomechanics and anterior corneal flattening. The operational procedure of theranostic-guided corneal phototherapy integrates the acquisition of molecular fluorescence emitted by excited riboflavin to assess its corneal concentration with a machine learning algorithm that processes molecular data in real time. This approach ensures optimal ultraviolet (UV) light photo-activation of riboflavin only when this substance is properly enriched in the corneal stroma under treatment, thereby improving the cross-linking process and reducing the risk of adverse effects, particularly when the corneal epithelium remains intact.[5–7] Notably, the multicenter, randomized clinical trial assessment of theranostic-guided riboflavin/UV-A corneal cross-linking for

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treatment of keratoconus, has demonstrated the promising results of theranostic-guided corneal phototherapy in treating keratoconus.[9] The trial confirmed the efficacy of this innovative approach, achieving 91% accuracy and 95% precision in predicting K_{max} flattening at 1 year after treatment. It also highlighted the procedure's safety and superiority over traditional transepithelial techniques in improving corneal topography K_{max} readings and visual outcomes. These evidence-based clinical findings proved that theranostic-guided corneal phototherapy could become a new gold standard in the treatment of ECD.

This manuscript focuses on the application of theranostic-guided transepithelial corneal phototherapy for treating ECD.

Materials and Methods

In this article, we report about three patients affected by ECD treated by a surgeon (ML) using the theranostic UV device (C4V CHROMO4VIS, Regensight srl, Italy), as described herein. Patients signed a written informed consent form prior to surgery; they provided written consent for inclusion of their anonymized clinical and imaging details for the purpose of publication. Ethical committee approval was not required since the study procedure did not include any medical or surgical approach to the patient (granted exemption). Treatments were performed under topical anesthesia; 0.4% lidocaine hydrochloride eye drops were instilled five times over 20 minutes before treatment. At the beginning of the treatment, after placing a lid speculum, the operator aligned and focused the Placido rings, which were projected by the active medical device, onto the cornea through the interaction with an augmented reality Graphic User Interface displayed on the touchscreen display. Once focusing was completed, the operator was invited to acquire an image of the cornea to treat by pressing the footswitch to activate a 3 mW/cm^2 UV-A light irradiance for 2 seconds. The measure was recorded as baseline corneal fluorescence signal from the UV-A theranostic device (i.e., baseline theranostic measure). Thereafter, the surgeon started applying one drop of 0.22% riboflavin ophthalmic solution (RitSight, Regensight srl) every 20 seconds onto the cornea for 20 minutes. Once the imbibition phase was completed, the cornea was irradiated by 10 mW/cm^2 UV-A power density for 9 minutes (5.4 J/cm^2 energy density); no riboflavin was applied over the corneal surface during UV-A light irradiation in any case. At pre-set time intervals, both during the imbibition and UV-A phototherapy phases, the UV-A theranostic device recorded the fluorescence images emitted by the cornea to estimate the riboflavin concentration and treatment efficacy, respectively.[6,7,9] The theranostic measurements were performed over a central area of the cornea by irradiating the cornea under treatment with 3 mW/cm^2 UV-A power density for 2 seconds (as for baseline measure); the theranostic device processed corneal fluorescence images in real time and provided the operator with an imaging biomarker estimating the corneal riboflavin concentration (the *riboflavin score*) and a calculated value estimating treatment efficacy (the *theranostic score*, which was calculated during UV phototherapy phase only).[6,7,9] The *riboflavin score* was calculated taking into consideration the central corneal thickness (CCT) value of the cornea and using a 2nd order polynomial function that depends on the green intensity signal acquired by the red green blue (RGB) camera of the theranostic device.[5–7] The *theranostic score* was calculated using a polynomial function that depends on the green intensity signals emitted by the cornea tissue before UV-A phototherapy (i.e., the last measurement of the dosing phase) and during the UV-A phototherapy; its value, expressed in dimensionless units.[6,7,9]

The cut-off values for predicting the propensity of theranostic treatment to flatten the corneal topography K_{max} value are a *riboflavin score* > 0.4 and a *theranostic score* ≥ 0.60, as validated in the ARGO trial.[9] At the end of the imbibition phase, if the *riboflavin score* has a value of ≤ 0.4, the theranostic device prompts the surgeon to extend the riboflavin application.[9] The UV-A light phototherapy phase begins once the corneal stroma is adequately enriched with riboflavin.

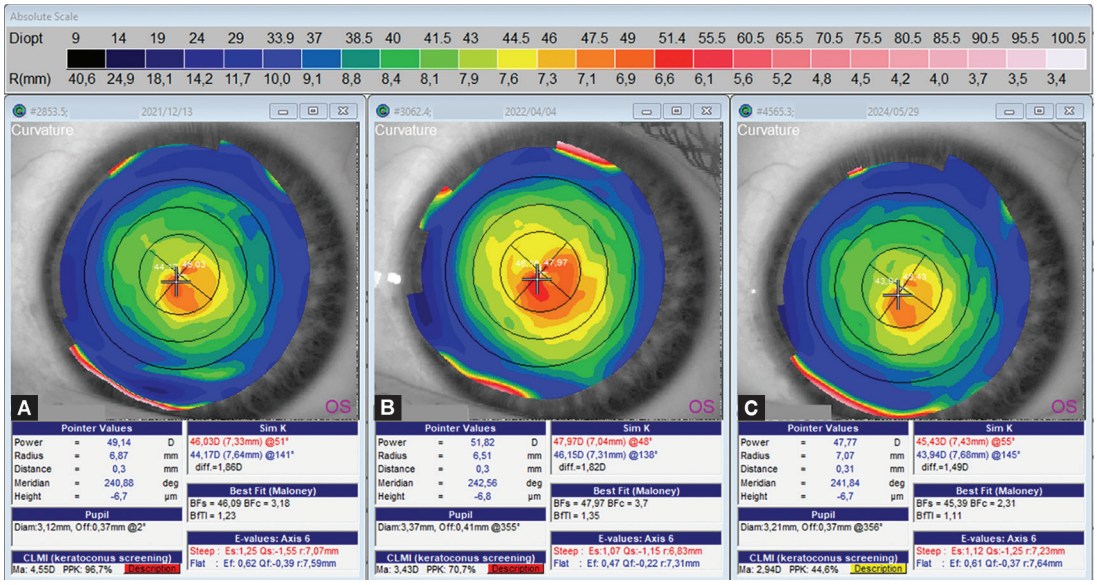
After treatment, patients were prescribed topical antibiotic (0.3% ofloxacin eyedrops) 3 times daily for 5 days, corticosteroid (0.2% fluorometholone eyedrops) 2 times daily for 21 days, and lubricant eye drops (0.2% sodium hyaluronate eyedrops) 6 times daily for 3 months.

Results

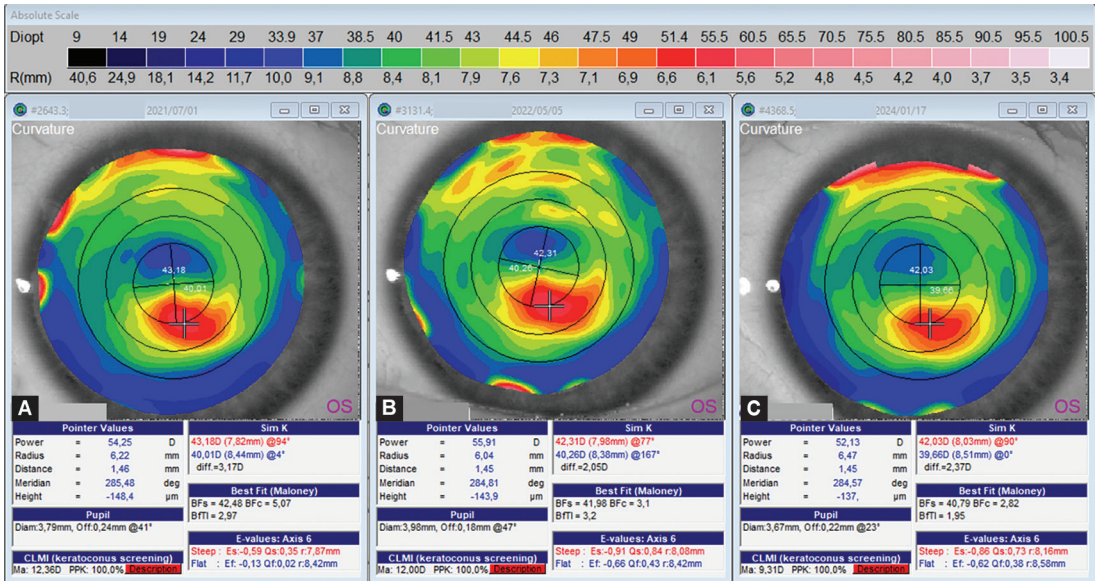
A 22-year-old male was referred to our clinic for blurry vision due to keratoconus. The patient reported a shellfish allergy and progressive deterioration of vision in both eyes in the last year. Although he was advised to undergo prompt treatment for keratoconus, he had to delay the intervention due to his university studies. Four months after the baseline visit, the patient returned to the clinic for treatment, showing a 2.7 D K_{max} steepening at the corneal topography (Keratron Scout, Optikon) of the left eye in comparison with the baseline visit. His manifest refraction in the left eye was +0.50 sphere −2.00 cylinder 120°, with uncorrected distance visual acuity (UDVA) of 0.8 LogMAR and corrected distance visual acuity (CDVA) of 0.1 LogMAR. The CCT was 516 µm (AS-OCT HS-100, Canon). Theranostic-guided transepithelial corneal phototherapy was completed successfully with *riboflavin score* and *theranostic score* of 0.42 and 0.90, respectively. Twenty-four months after treatment, his manifest refraction in the left eye was −1.50 cylinder 130°, with UDVA of 0.3 LogMAR and CDVA of −0.1 LogMAR. The K_{max} value flattened by 4.0 D, and the CCT was 539 µm. Corneal total high-order aberrations (HOA) decreased from 1.00 to 0.83 µm (17% decrease) from preoperatively to 24 months postoperatively. Figure 1 depicts the corneal topography maps from baseline to 24-month postoperative visits in this case study.

A 29-year-old male patient was referred to our clinic due to keratoconus. The patient reported a previous standard CXL treatment in his left eye four years earlier the baseline visit at our center. The patient had no previous medical records and was advised to attend regular follow-up visits. Ten months after baseline visit at our center, the corneal topography showed 1.7 D K_{max} steepening, CCT thinned by 23 µm, and CDVA decreased by 1 early treatment diabetic retinopathy study (ETDRS) line in his left eye in the same period. His manifest refraction in the left eye was −6.00 sphere, with CDVA of 0.6 LogMAR. The CCT was 488 µm. Theranostic-guided transepithelial corneal phototherapy was completed successfully with *riboflavin score* and *theranostic score* of 0.48 and 0.72, respectively. Eighteen months after treatment, his manifest refraction in the left eye was −5.25 sphere, with CDVA of 0.0 LogMAR. The K_{max} value flattened by 3.8 D, and the CCT was 501 µm. Corneal total HOA decreased from 2.02 to 1.57 µm (23% decrease) from preoperatively to 18 months postoperatively. Figure 2 depicts the corneal topography maps in this case study.

A 52-year-old female patient was referred to our clinic due to reporting ocular discomfort and mild conjunctival hyperemia in her

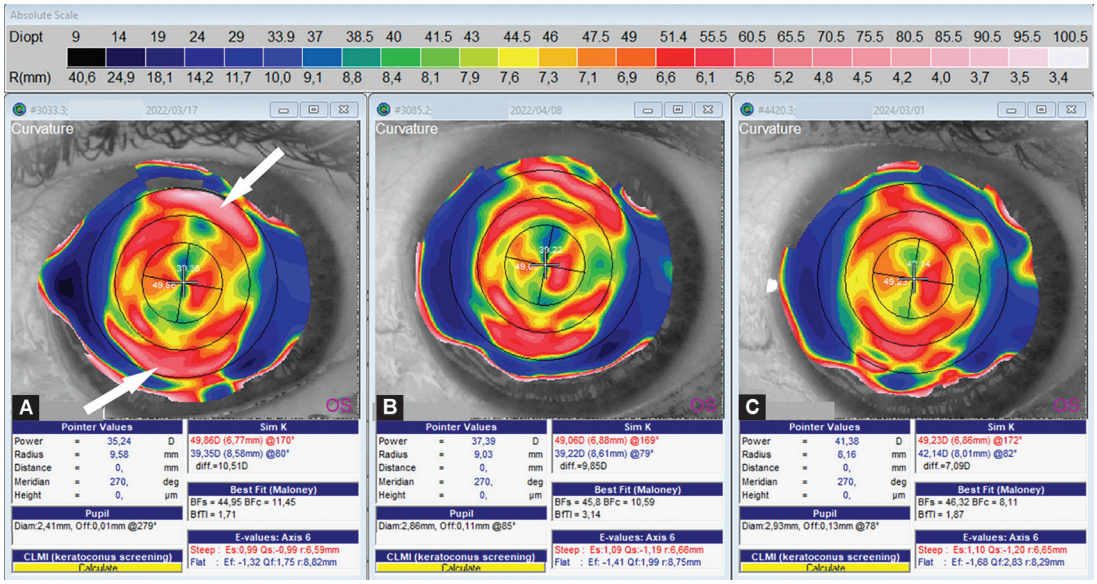


Figs 1A to C: Corneal topography tangential maps of the left eye ("OS") of a 22-year-old male affected by keratoconus. In (A) baseline acquisition; in (B) preoperative acquisition, taken 4 months after baseline visit, showing K_{max} reading that steepened by 2.7 D in the same period. In (C) 24-month follow-up acquisition after theranostic-guided transepithelial corneal phototherapy showing a 4.0 D K_{max} flattening in comparison with preoperatively. Following treatment, the anterior cornea showed a significant decrease in the ectatic area



Figs 2A to C: Corneal topography tangential maps of the left eye ("OS") of a 29-year-old male affected by keratoconus. The left eye was operated by standard CXL four years before the baseline visit (A). In (B) preoperative acquisition, taken 10 months after baseline visit, showing K_{max} reading that steepened by 1.7 D in the same period. In (C), an 18 months follow-up acquisition after theranostic-guided transepithelial corneal phototherapy showing 3.8 D K_{max} flattening in comparison with preoperatively. The regularity of the anterior cornea markedly improved after treatment, with Best-Fit Topographic irregularity index (BFTi) decreasing from 3.2 preoperatively to 1.9 postoperatively

left eye. She reported radial keratotomies (RK) for correction of high myopia and astigmatism 25 years earlier. At slit lamp examination, there were eight radial and two arcuate keratotomies, with these astigmatic incisions generating corneal ectasia. Her manifest refraction in the left eye was −2.00 sphere −4.50 cylinder 70°, with CDVA of 0.6 LogMAR. Theranostic-guided transepithelial corneal phototherapy was completed successfully with *riboflavin score* and *theranostic score* of 0.44 and 1.08, respectively. Twenty-four months after treatment, her manifest refraction in the left eye was −1.00 sphere −6.00 cylinder 80°, with CDVA of 0.2 LogMAR. The steepest corneal readings at the superior and inferior arcuate keratotomies decreased from 96.8 D and 72.2 D preoperatively to 74.6 D and 61.6 D postoperatively, respectively. Corneal total HOA decreased from 7.14 to 4.25 µm (40% decrease) from preoperatively to 24 months postoperatively. Figure 3 depicts the corneal topography maps during follow-up in the study case.



Figs 3A to C: Corneal topography tangential maps of the left eye ("OS") of a 52-year-old female with a diagnosis of post-RK corneal ectasia at the site of arcuate incisions (A; arrows). In (B) and (C), 1-month and 24-month postoperative acquisitions show the immediate and long-term response of the cornea to theranostic phototherapy, respectively. Two years after treatment, corneal astigmatism decreased by 3.4 D

Discussion

This study provided insights into the efficacy and safety of theranostic-guided transepithelial corneal phototherapy for ECD, even in the case of failed standard CXL treatment for keratoconus and iatrogenic corneal ectasia after RK for high myopia. The results presented in this cohort evidenced that theranostic-guided transepithelial corneal phototherapy offers a promising approach to managing these challenging conditions, with high safety and significant improvements observed in visual acuity over a 2-year follow-up period. The corneal topography and corneal aberration maps also demonstrated significant corneal flattening and reductions in total high-order corneal aberrations following treatment, which correlate directly with improved visual performance. Changes in corneal topography, although without a decrease of corneal HOA to the same extent, have been well documented in studies assessing conventional CXL for treatment of ECD.[3,4] The theranostic-guided transepithelial method used here potentially enhances these effects by providing a safer and more personalized and precise procedure, reducing the risk of sight-threatening complications, such as corneal infection and scars.[10]

The follow-up period of up to two years also provides valuable data on the long-term stability of the treatment. Previous studies have demonstrated that the effects of standard CXL are sustained over several years, with retreatment rates ranging between 14 and 25% over 15-year follow-up.[11–13] One of the patients in this cohort was treated 5 years after standard epithelium-off CXL due to manifest corneal steepening (1.7 D K_{max} steepening) measured over a 1-year follow-up at our center. Notably, the long-term outcome after theranostic-guided corneal phototherapy showed marked improvement in visual acuity with K_{max} reading that was 3.8 D flatter than preoperatively.

This study presents a limited case series and, as such, lacks the generalizability of larger clinical trials. The results should, therefore, be interpreted with caution. More robust and validated data on theranostic-guided corneal phototherapy are available in the ARGO clinical trial publication.[9]

Conclusion

This case series highlights theranostic-guided transepithelial corneal phototherapy as an effective and safe treatment for keratoconus, iatrogenic corneal ectasia, and keratoconus retreatment after standard CXL failure. The significant improvements in visual acuity, corneal topography, and corneal high-order aberration map, coupled with the absence of any long-term adverse events, indicate that this technique may offer long-lasting benefits to patients and has the potential to become a key tool in the management of ECD. Clinical studies with larger sample sizes and more diverse populations are ongoing and will help to identify patient-related or procedural factors that influence treatment success and guide clinicians in optimizing patient selection for this personalized corneal therapy.

Clinical Significance

Theranostic-guided transepithelial corneal phototherapy offers a safe and effective treatment for keratoconus, iatrogenic corneal ectasia, and retreatment after standard CXL failure, leading to significant improvements in vision and corneal parameters. Its personalized approach shows promise for managing complex corneal conditions, with ongoing studies set to enhance patient outcomes on a personal basis.

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