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CORRESPONDENCE

On the Overinterpretation of Theranostic Claims in Corneal Cross-Linking

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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

To the Editor

We read with interest the review by Roszkowska and Lombardo [1] addressing the role of theranostic technology in corneal cross-linking (CXL). While the integration of diagnostic feedback into therapeutic procedures represents an appealing conceptual advance, several key statements in the manuscript appear to overstate the current level of scientific validation and warrant critical clarification.

A central claim of the review is that real-time monitoring of intracorneal riboflavin concentration enables "precise therapeutic dosing" and "predictable outcomes" on an individual basis [1]. However, this assertion relies on the implicit assumption that intracorneal riboflavin concentration can be quantitatively determined in vivo through optical measurements. This assumption is not adequately substantiated. In scattering biological tissues, fluorescence signals are inherently affected by multiple confounding factors – including light scattering, absorption heterogeneity, stromal hydration, and dynamic structural changes during irradiation – preventing a direct and quantitative relationship with chromophore concentration [2,3]. Moreover, riboflavin undergoes continuous photodegradation and participates in oxygen-dependent reactions during UV-A exposure, further decoupling fluorescence intensity from actual stromal concentration [4,5]. Under such conditions, fluorescence should be regarded as, at best, a qualitative indicator rather than a quantitative biomarker.

The manuscript further suggests that theranostic systems can dynamically adjust UV-A delivery based on these measurements to achieve "precise" and "personalized" treatment [1]. Yet, no validated physical or photochemical

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model is presented to demonstrate that this signal corresponds to a well-defined or controllable variable within the cross-linking process. In the absence of such validation, the use of indirect optical signals to guide energy delivery risks introducing variability rather than improving standardization.

Particular caution is also required in the interpretation of the ARGO trial, which is presented as providing "robust evidence" of predictive accuracy and treatment precision [1]. These outcomes refer to postoperative topographic changes (e.g., Kmax), which are influenced by multiple biomechanical and healing-related factors. Their use to support real-time control of riboflavin concentration or UV-A dosing is therefore not justified. Correlation with clinical outcomes does not demonstrate control over the underlying photochemical kinetics.

More broadly, the manuscript reflects an attempt to personalize treatment through indirect surrogate measurements rather than through rigorous modelling of the physical and chemical mechanisms governing CXL. The efficacy of cross-linking depends on the interaction between UV-A irradiance, riboflavin photochemistry, and oxygen availability, which follow defined kinetic principles [6,4]. Approaches based on first-principles modelling of these interactions allow the required fluence to be calculated directly and provide a reproducible framework that permits treatment to be standardized, without reliance on uncertain optical surrogates.

In conclusion, while theranostic technology represents an interesting research direction, the current evidence does not support the claim that intracorneal riboflavin concentration can be reliably quantified in vivo or that such measurements can be used to precisely guide UV-A dosing. A more cautious interpretation grounded in validated physical models is required before these concepts can be translated into clinical practice.

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