

# A New Alternative to Riboflavin/Ultraviolet-A: Collagen Cross-Linking With Rose Bengal/Green Light

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Corneal cross-linking (CXL) with ultraviolet-A (UVA) and riboflavin has been used increasingly during past decades. There is strong evidence of its effect on stabilizing the biomechanics of the cornea, so it has become the gold standard for treatment for slowing the progression of keratoconus and post-laser-assisted in situ keratomileusis (LASIK) corneal ectasia. Riboflavin serves as a photosensitizer. When it is activated by UVA radiation, oxygen radicals are released into the corneal stroma, followed by formation of new covalent bonds between collagen fibrils, thereby stiffening the corneal stroma.<sup>1</sup>

In this issue of IOVS, Bekesi et al.<sup>2</sup> investigated a new photochemical procedure using rose bengal and green light (RGX) as an alternative to CXL with riboflavin and UVA (UVX). They hypothesized that this new technique might overcome some of the drawbacks of CXL, including dehydration of the cornea, cytotoxicity to keratocytes, and the high percentage of corneal thickness that must be treated to get the desired effect. In their study, they compared the biomechanical corneal response of two different CXL treatments, RGX and UVX using an imaging technique that involves air-puff deformation in rabbit eyes.<sup>2</sup>

The investigators demonstrated that both techniques stiffened the cornea. Even though the deformation parameters revealed overall greater stiffening after UVX, the subjects that received RGX seemed to have more effective stiffening in the layer of cornea that was cross-linked (100  $\mu\text{m}$  in RGX and 137  $\mu\text{m}$  in UVX).<sup>2</sup> They attributed this finding to a difference in the covalent cross-links produced by the two photosensitizers after irradiation, since the cross-links are located at different molecular level sites in the corneal stroma.<sup>2</sup>

Because of its lower effect on corneal thickness than the standard riboflavin with dextran, and its shallower penetration into stroma, RGX seems to help us to treat corneas less than 400  $\mu\text{m}$ .<sup>2</sup> Additionally, while dextran remained in the cornea during the CXL with riboflavin and UVA, and might affect the deformation parameters after irradiation, rose bengal is partially destroyed during RGX and, thus, might have less of an influence on deformation parameters after irradiation.<sup>2</sup> The authors also claimed that rose bengal alone, without irradiation, could increase the corneal stiffening, as documented previously.<sup>3</sup>

In conclusion, these findings highlighted the importance of investigating alternative photosensitizers and illumination sources that may have higher efficacy and lower complications rates compared to the standard CXL method. As the authors discussed, the optimal penetration depth that maintains the balance between corneal treatment response and endothelial protection must be addressed in further studies.

## References

1. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135:620-627.
2. Bekesi N, Kochevar IE, Marcos S. Corneal biomechanical response following collagen cross-linking with rose bengal/green light and riboflavin/UVA. *Invest Ophthalmol Vis Sci*. 2016;57:992-1001.
3. Cherfan D, Verter EE, Melki S, et al. Collagen cross-linking using rose bengal and green light to increase corneal stiffness. *Invest Ophthalmol Vis Sci*. 2013;54:3426-3433.

