Author Response: Analytic Formulas on Factors Determining the Safety and Efficacy in UV-Light-Sensitized Corneal Cross-Linking

We thank Jui-Teng Lin[1] for his interest in our recent work studying riboflavin (RF)-UVA–assisted corneal collagen cross-linking (CXL).[2] His comments on our data with a mathematic equation bring new perspectives to the corneal CXL biology.

Since RF-UVA CXL emerged as a medical alternative to treat corneal ectatic disorders, efficacy and safety have been the central topics for laboratory and clinical research.[3,4] In photo-assisted CXL, the efficacy depends on both the RF tissue dose and the irradiation of UVA. How the depth-resolved profiles of RF and UVA affect CXL efficacy remains unclear. In our recent work,[2] we profiled the tissue distribution of various RF doses by confocal fluorescence microscopy. The corneal absorption of RF was positively related to the administered RF dosage. Interestingly, the saturation zone (RF penetration depth) was found to be localized in a stromal depth from 150 to 300 μm. Consistent with our findings, Mastropasqua et al.[5] used HPLC to demonstrate that 80% of RF was absorbed by the first 300 μm corneal stroma. In parallel, an increase in UVA irradiation dose leads to a higher CXL efficacy, as demonstrated by Chai et al.[6] Lin's mathematical formula, $R(z,t) = 2a\phi I(z,t)C(z,t)$, successfully models such RF-UVA-mediated CXL photokinetics.[1] The efficacy of CXL indicated by Lin's "normalized RF concentration" profile was positively correlated to UVA dosage.

Using second harmonic generation (SHG) microscopy, we further reported that the most effective zone of RF-UVA CXL was confined to 150 to 250 μm irrespective of RF dosage.[2] In comparison, Chai et al.[6] indicated that the effective CXL region was restricted to the anterior 300 μm and not correlated to the UVA irradiation dosage. Such a depth threshold of CXL is well explained by Lin's formula. Analytically, he shows that the dose effect of UVA irradiation for CXL mainly takes place in a stromal depth of 150 to 250 μm.

Clinically, the safety range between therapeutic and phototoxic UVA irradiation doses is largely reduced when CXL treatment is applied to thin corneas with a limited UVA penetration depth. As commonly accepted, the safety threshold for corneal thickness in CXL therapy is set to be 400 μm. The effective CXL zone up to 300 μm, collectively supported by our SHG image data, Mastropasqua's HPLC results, and Lin's mathematical model, justifies such a case selection criterion. Future laboratory studies will merit the clinical ramification of Lin's mathematical CXL model.

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