Corneal Collagen Cross-linking in Bullous Keratopathy

To the Editor:

In their article, which was published in the September 2008 issue of the *Journal of Refractive Surgery*, Krueger et al[1] detailed their use of an adapted version of Wollensak et al's[2] corneal collagen cross-linking (CXL) therapy to treat a patient with bullous keratopathy. Although the patient's symptoms appeared much improved at 6-month follow-up, the safety of such a treatment, in which riboflavin is injected into superficial and deep stromal layers of the cornea and subsequently exposed to high-level ultraviolet A (UVA) irradiance, is a cause for concern.

In standard corneal collagen CXL therapy, UVA of irradiance 3 W/cm^2 is applied to the de-epithelialized surface of a riboflavin-soaked cornea for 30 minutes.[2] This recommended UVA irradiance level is based on the results of multiple scientific experiments aimed at optimizing the safety and efficacy of the procedure.[3-6] Experimental data have shown that increasing the irradiance level above 3 mW/cm^2 results in endothelial cell death[3,4] and an increased loss of keratocytes throughout the cornea.[5] However, the toxicity effect of two doses of 15 mW/cm^2 UVA irradiance each lasting 7 minutes (one dose for each stromal pocket), as used by Krueger et al[1] to treat a patient with bullous keratopathy, is currently unknown. Furthermore, as the rate of riboflavin photodegradation has not yet been investigated, it is not clear whether a single intrastromal injection of riboflavin prior to a 7-minute exposure to high-level UVA is sufficient to prevent damage to the deeper ocular structures. Based on current scientific research, it seems likely that the treatment described in this article would cause significant damage both to keratocytes and endothelial cells. In our opinion, it is dangerous to perform such a procedure until its safety has been established, and this is especially true in cases of bullous keratopathy in which the endothelial layer is already compromised.

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Reply:

Drs Hayes and Kamma-Lorger make an important point; however, I have a few points to add.

The potential toxicity of ultraviolet (UV) light at the endothelial level studied in previous reports refers to riboflavin "soaked" cornea following multiple riboflavin solution drops.[1-7] We previously studied and presented the laboratory effect of UV light alone in cadaver corneas.[8] In this laboratory experiment, we proposed that the amount of corneal deturgescence may be viewed as the clinical index of the degree of collagen cross-linking (CXL) achieved. Ultraviolet light alone did not appear to have a significant effect in reversing swelling in these corneas, therefore we assume "little" CXL was conducted, hence no significant cytotoxic effect. It is the presence of riboflavin at various levels of the cornea that absorbs the applied UV light, making exposure to such fluence of UV irradiation potentially harmful to keratocytes and/or endothelium. We therefore theorize that in a very "thick" cornea, there is poor penetration of riboflavin—applied topically—as well as UV light to the deeper corneal layers.

In contrast to a normal cornea with minimum 520- to 540-µm thickness, a cornea with chronic bullous keratopathy, due to endothelial cell failure, usually is >700-µm thick. This makes the attempt of cross-linking the anterior layers of such a swollen cornea with bullous keratopathy potentially safer than in a normal cornea, as we are working on the outer-half of the cornea. Furthermore, pre-existing significant endothelial cell loss in these corneas (the pathogenesis of bullous keratopathy) offers no hope for the recovery of endothelial cell viability. We therefore believe that endothelial toxicity is not a significant concern in these cases, in contrast to much thinner, compact keratoconic eyes.

The traditional CXL technique failed in our experience to provide significant corneal deturgescence in bullous keratopathy, as it appears to affect mainly the anterior 300 µm of cornea—as expected based on previous studies[9]—with minimal beneficial clinical effect for the middle and deeper cornea swelling, which may result in pain and recurrent epithelial defects. Our novel technique was therefore designed to potentially cross-link a "broader" thickness and deeper layers of these corneas.

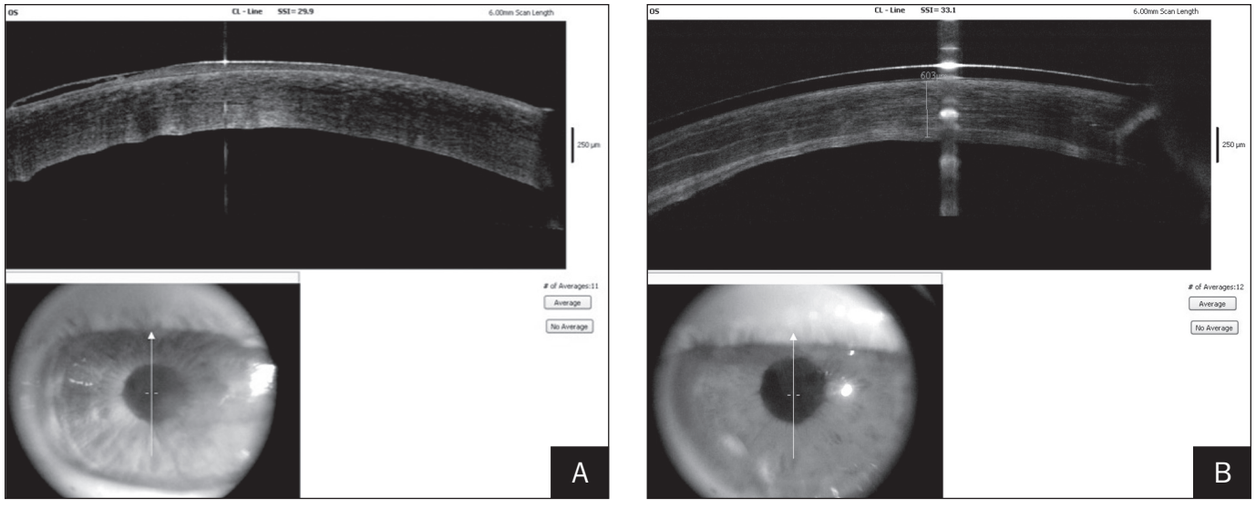

Figure. A) Corneal optical coherence tomography (Optovue Inc, Fremont, Calif) in a cornea with bullous keratopathy showing marked stromal swelling and an epithelial detachment. **B)** The same cornea 1 day after sequential femtosecond laser–assisted intrastromal cross-linking at 350 and 150 μm. The corneal stroma is compact and the "pocket" interface remnants are clearly visualized as hyperreflective lines in the cornea stroma. The tissue is clearly more lucent.

As clinicians, we are familiar with alternative options for such a patient, which consist of a penetrating graft (endothelial keratoplasty or Descemet's stripping endothelial keratoplasty [DSEK] would be challenging due to stroma opaqueness). As a result, the patient's host cornea would end up at the histology lab, at no help to the patient.

An additional advantage of our technique is the possibility that by making the bullous cornea more compact and gaining cornea clarity, a less invasive procedure than penetrating keratoplasty or DSEK may be facilitated for this patient.

We do not believe this technique provides a long-term solution, but it may be helpful in alleviating severe symptoms of pain and epithelial erosion for several months, enabling the patient to delay and/or postpone more invasive and costly surgical options.

The Figure demonstrates pre- and postoperative optical coherence tomography images that illustrate our technique.

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