Accelerated Corneal Cross-Linking: We Must Acquire Knowledge as Fast

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Corneal cross-linking (CXL) represents a true innovation in the treatment of corneal ectatic disorders and remains a topic of great interest to the readership of the *Journal of Refractive Surgery*, perhaps even more so now that the treatment has finally been approved by the U.S. Food and Drug Administration for use in the United States. Over the past year alone, numerous studies have been published evaluating modifications in protocols to determine equivalence between treatments and identify the optimal combination of riboflavin and ultraviolet light to induce the CXL effect. With that in mind, it seems appropriate to take a moment to review what we do and do not know or understand about CXL as we seek these optimized protocols.

DIFFERENT PROTOCOLS MEANING DIFFERENT INFORMATION

The standard protocol for CXL, riboflavin stromal saturation followed by application of ultraviolet light at 3 mW/cm^2 for 30 minutes, which corresponds to a total energy dose (fluence) of 5.4 J/cm^2, has been widely applied and investigated for the management of progressive ectatic disorders. Faster options, with higher fluence and reduced exposure time to maintain a near constant total irradiance and efficacy according to the photochemical law of reciprocity, have been termed accelerated CXL (aCXL). Although theoretically equivalent, these treatment protocols may not necessarily have the same impact on the cornea.

The Bunson–Roscoe law of reciprocity states that the equivalent photochemical effect can be achieved with any combination of fluence intensity and time as long as the overall irradiance is equal. Thus, proportionally reduced illumination time and correspondingly increased irradiation intensity, the accelerated protocols, should be as efficacious as the standard protocol. The mathematics behind it seems simple because 1 joule (J) = 1 watt (W) × second (s), so 3-minute irradiation at 30 mW/cm^2 (180 s × 0.03 W = 5.4 J), 5 minutes at 18.0 mW/cm^2 (300 s × 0.018 W = 5.4 J), or 10 minutes at 9.0 mW/cm^2 (600 s × 0.009 W = 5.4 J) should all deliver the same 5.4 J/cm^2. However, the biological response to these alterations may not be as simple.

Even if the photochemical effect is similar, compressing energy in time potentially translates into a wide variety of biological response, from different levels of cell death to a range of change in collagen fibers. The *Journal of Refractive Surgery* recently published a study[1] revealing that a higher energy (7.2 J) may be necessary to achieve the equivalence. A full comprehension of lasting changes associated with either a shorter exposure time to achieve the same 5.4 J or higher total energy is still needed to dismiss long-term concerns.

Until this point, different protocols with different exposure times that may or may not present the same biomechanical impact and even different fluencies have all been grouped as aCXL, as a synonym of the same approach where they apparently induce singular modifications and consequences to the cornea. Perhaps that grouping is not as accurate as it has been portrayed. To answer that question, answers to some fundamental aspects of the CXL process must be determined.

WHAT DOES THE DEMARCATION LINE DEMARCATE?

The demarcation line has been used as a surrogate marker for depth of effect after CXL.[2] But are we sure that is what it indicates?

Studies have yet to confirm whether all of the tissue truly modified is marked by the line.[3] To date, no threshold depth after which the CXL efficacy is achieved has yet been fully established. Perhaps rather than an absolute number (ie, demarcation line depth in microns)

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it may be more useful to measure the percentage of the cornea that has been cross-linked or biomechanically modified. Given these unanswered questions, should the shallower demarcation line after aCXL compared to the standard protocol really be automatically translated into reduced CXL efficacy?

Different studies reveal that, despite a shallower demarcation line, aCXL is still able to halt the progression of the disease.[3] If it does represent the level of CXL biological alteration, a more superficial action (if still effective) may also mean a safer option for eyes with thin corneas (if indeed presenting a lasting effect),[4] farther from the endothelium.

CORNEAL REMODELING AND WOUND HEALING IN CXL

According to the Lambert–Beer law, the deeper in the tissue the ultraviolet light travels, the more attenuated it will become. Therefore, theoretically, the accelerated approach would not only represent less risk for the endothelium but also, being more superficial, less keratocyte death, because even less energy will reach the posterior stroma compared to the standard protocol.

Because the effective depth of CXL has also been implicated as part of the explanation of corneal remodeling and flattening associated with this procedure[5] and because the long-term corneal changes are not always a positive side effect, a shallower effect could be a step toward a more controlled treatment.

THE ROLE OF OXYGEN IN DETERMINING OPTIMAL TREATMENT TIMES

Higher oxygen consumption in accelerated protocols leading to oxygen depletion in the stroma is one of the main theories that could explain a shallower effect. Despite some facts that would account for a longer time for oxygen replenishment, pulsed protocols with aCXL delivering ultraviolet light with an on-off pattern could allow a better diffusion of the oxygen into the corneal stroma and subsequent deeper effect.[6,7] Questions remain about the best combination of on and off time and the associated energy with which it would perfectly match to achieve a (still) safe and more efficient procedure.

ACCELERATING OUR KNOWLEDGE OF ACCELERATED PROTOCOLS

We should recognize different biological responses to different aCXL fluences, better determine the percentage of tissue that should be marked as the threshold for efficacy and its correct, and actual, correlation with demarcation line, comprehend the association of a shallower effect with remodeling and wound healing, and evaluate the role of oxygen and its relationship with potential optimal treatment exposure times. The *Journal of Refractive Surgery* has propagated the evidence-based medicine and kept up with the relevant studies in this particular field. As the method to halt ectasia progression accelerates and rapidly evolves, we must acquire knowledge as fast.

REFERENCES

1. Kymionis GD, Tsoulnaras KI, Liakopoulos DA, et al. Corneal stromal demarcation line depth following standard and a modified high intensity corneal cross-linking protocol. *J Refract Surg.* 2016;32:218-222.
2. Seiler T, Hafezi F. Corneal cross-linking-induced stromal demarcation line. *Cornea.* 2006;25:1057-1059.
3. Medeiros CS, Giacomin NT, Bueno RL, Ghanem RC Moraes HV Jr, Santhiago MR. Accelerated corneal collagen crosslinking: technique, efficacy, safety and applications. *J Cataract Refract Surg.* In press.
4. Ozgurhan EB, Akcay BI, Kurt T, Yildirim Y, Demirok A. Accelerated corneal collagen cross-linking in thin keratoconic corneas. *J Refract Surg.* 2015;31:386-390.
5. Santhiago MR, Giacomin NT, Medeiros CS, Smadja D, Bechara SJ. Intense early flattening after corneal collagen cross-linking. *J Refract Surg.* 2015;31:419-422.
6. Peyman A, Nouralishahi A, Hafezi F, Kling S, Peyman M. Stromal demarcation line in pulsed versus continuous light accelerated corneal cross-linking for keratoconus. *J Refract Surg.* 2016;32:206-208.
7. Kling S, Richoz O, Hammer A, et al. Increased biomechanical efficacy of corneal cross-linking in thin corneas due to higher oxygen availability. *J Refract Surg.* 2015;31:840-846.