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Editorial

Corneal Cross-linking for Keratoconus: A Look at the Data, the Food and Drug Administration, and the Future

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In the cornea, cross-linking occurs naturally with aging because of an oxidative deamination reaction that occurs within the end chains of collagen.[1] The use of riboflavin as a photosensitizer to generate reactive oxygen species when activated by ultraviolet light to form these cross-links artificially was described first in the late 1990s in animal studies.[2] Subsequently, Wollensak et al[3] reported on this procedure, now widely known as corneal cross-linking (CXL), for the treatment of keratoconus in humans in 2003.

Since then, hundreds of reports have been published on the use of CXL for treating keratoconus, as well as for many other conditions such as other ectasias and infectious keratitis. Although CXL has been approved for use in Europe since January 2007, it was not approved for use by the United States Food and Drug Administration (FDA) until April 18, 2016, for the indication of keratoconus. Very recently, on July 19, 2016, CXL was approved by the FDA for the treatment of corneal ectasia after refractive surgery. What took so long?

The controversy over the FDA approval process for CXL was centered on the available data.

Despite seemingly overwhelming evidence from anecdotal reports and prospective studies on the safety and efficacy of CXL, the data were inconsistent and not as strong as they may have seemed. Some of this inconsistency stemmed from variability in protocols and techniques. At the February 24, 2015 FDA joint meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee and the Ophthalmic Devices Panel of the Medical Devices Advisory Committee,[4] the panel of experts was presented with data from 3 prospective, randomized, open-label, controlled clinical trials of CXL sponsored by Avedro, Inc. (Waltham, MA). After extensive discussion, including statements made by consumer representatives and leaders from our ophthalmic professional societies, the panel was asked to vote on 2 specific questions. The first question was whether substantial evidence of efficacy and safety for the drug-device combination of Photrexa viscous and Photrexa (riboflavin ophthalmic solution), and the KXL System (ultraviolet light) (Avedro, Waltham, MA) to support approval for progressive keratoconus had been shown. Despite numerous panel members stating that the data and analysis were imperfect, and even that the study design had major issues, most members voted in favor (10 yes, 4 no, 1 abstention) because of an "unmet need" for the treatment of this condition. One member who voted against stated that he wanted to approve this, but based on the data and study design, could not. Many members also were troubled by the request to approve a device (ultraviolet light source) that was not actually the same device that was used in the studies (same technology, but different device).

The second question asked was whether substantial evidence of efficacy and safety for the drug-device combination of Photrexa viscous and Photrexa, riboflavin ophthalmic solution, and the KXL System, ultraviolet light, to support approval for corneal ectasia following keratorefractive surgery had been demonstrated. Although voting was still in favor of approval (6 yes, 4 no, and 4 abstentions, [only 14 votes as one member was not able to stay for voting]), members made similar comments as for the first question, and more abstained because of smaller amounts of data for this proposed population, but were reluctant to vote no, likely because of the unmet need for this technology.

With the votes and these comments from the panel in mind, in March 2015 the FDA denied approval and requested additional information from the sponsor. Ultimately, on receipt of additional information and rereview, FDA approval was obtained on April 18, 2016, for keratoconus, and then on July 19, 2016, for corneal ectasia after refractive surgery. But what actually transpired during this 1 year at the FDA that ultimately led to approval? And why did it take nearly 10 years of trials in the United States for the FDA to approve?

From a report from one of the authors (B.H.J.) who was at the meeting on the FDA panel and from a review of the transcripts from the meeting, it was clear that there were concerns over the data presented. In addition to what some deemed as excessive amounts of missing data points, the analysis of the data also was called into question, and this was highlighted by the timing of the development of the statistical analysis plan. The first clinical trial presented by the sponsor actually mostly was completed in 2010 before the sponsor had acquired the product from a previous company. The other 2 studies were completed in the first half of 2011, but the statistical analysis plan was not actually finalized until late 2011 or early 2012, after the last participant completed the study. In fact, a portion of the study results was submitted for publication in March 2010, before finalization of the statistical analysis plan.

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This struggle for adequate data also is reflected in the literature: whereas numerous studies have been published on this topic, meta-analyses reveal conflicting results. In a recent systematic review and meta-analysis, Meiri et al[5] analyzed 75 publications on the use of CXL in keratoconus, and they concluded that CXL is safe and effective for halting the progression of keratoconus. However, the analysis included mostly retrospective studies, many of which had small sample sizes and short follow-up. In contrast, in a recent Cochrane Database review, Sykakis et al[6] evaluated 3 randomized controlled trials that enrolled a total of 225 eyes and found that there was limited evidence for CXL in the management of keratoconus because of the lack of properly conducted randomized clinical trials. The authors specifically cited that the "quality of the evidence was very low because of problems in the way the studies were done and reported and the small number of eyes included."

Was it just the data that were troublesome, however, or was there more? The manner in which some of the CXL trials in the US were implemented was a departure from how clinical trials generally are administered. Standard trials go through a stringent institutional review board review process that carefully reviews protocols and consent forms to ensure that potential trial participants are not coerced into participation by monetary rewards or undue influence of investigators. Some of the previous CXL trials were quite the opposite: based on the trial center, some potential subjects were required to pay for the treatment to participate, and therefore, those without adequate financial means potentially were turned away from participating, unless the center was willing to pay the cost. In fact, approximately 80% of the sham eyes in some studies ultimately crossed over to have CXL performed, most often at 3 or 6 months, sometimes requiring payment. This is exactly the type of situation that our current ethical standards for research should prevent: those with lesser means not having access to potential treatment.

Furthermore, in some of the previous CXL trials, some investigators were required to purchase the equipment to perform the CXL. As such, the site-to-site variability, whereby some centers were given the equipment and other sites had to pay for equipment, altered the way patients were recruited and potentially introduced significant selection bias.

So what actually happened at the FDA? As noted above, there were many concerns over the quality of the data, including the definition of progression of keratoconus (progression is implied for corneal ectasia after keratorefractive surgery) and small sample sizes. But these concerns did not stop the approvals for these indications. Although highly convincing data may be limited at this time, it is true that CXL for corneal ectasias fulfills an unmet need; indeed, there is no other treatment option available to slow or halt disease progression. But does an unmet need for a particular condition override the need for rigorous clinical trial implementation and validity of the data? This is an important distinction to consider, because the FDA panel meeting did not ask whether there was a need for this technology, but whether there was evidence that this technology was efficacious. But now that CXL is finally approved in the United States, what does that mean for us?

Halting the progression of keratoconus conceivably could prevent entirely the need for progression to surgical intervention (currently quoted at 10%−20% of all patients with keratoconus). In fact, 2 recent studies already have suggested that the use of CXL has decreased the number of corneal transplants for keratoconus in Norway[7] and in the Netherlands[8] when looking at periods before and after CXL. According to the 2015 data from the Eye Bank Association of America, 6679 penetrating and anterior lamellar keratoplasties were performed for the diagnosis of keratoconus of 72 465 total keratoplasties (9.2%) using tissue distributed from United States eye banks (and mostly used in the United States).[9] The potential impact of CXL on corneal transplantation in the United States thus could be significant, allowing for more tissue to be available for other indications or for exportation abroad. A similar shift occurred when phacoemulsification machines and techniques improved significantly and the rate of pseudophakic bullous keratopathy then declined significantly, allowing for more availability of corneal tissue for other uses. The impact of CXL on corneal transplantation could be even more profound in areas such as the Middle East and New Zealand, where the prevalence of keratoconus is much higher than in the United States. Additionally, in countries where tissue availability is very limited and eye banking is not established, CXL for keratoconus can alter the course of these patients' lives because they never would have been able to obtain a transplant.

Although keratoconus was first described by Benedict Duddell in 1736, we have experienced only recently an explosion of information regarding this condition. Through 1994, there were approximately 750 peer-reviewed publications on keratoconus, and this increased to more than 5000 through 2014.[10] Much of this newer literature concerns the treatment of keratoconus. Although outcomes of penetrating keratoplasty generally are very good for keratoconus, deep anterior lamellar keratoplasty has become more popular in the last 2 decades, and it offers the ability to prevent endothelial rejection, theoretically improving the longevity of the grafts. Intracorneal ring segments have become popular in the last decade, and they are purported to reshape keratoconus eyes and possibly delay keratoplasty. New improvements in contact lenses, including hybrid lenses, rigid gas permeable lenses, and scleral lenses, have delayed further or possibly prevented the need for keratoplasty; this possibility is real and was not addressed in the previously mentioned studies from Norway[7] and the Netherlands.[8] And now, CXL may revolutionize the way we manage keratoconus further.

The practice of medicine, and ophthalmology, is and should be data driven. That said, should poorly designed studies and suboptimal analysis of data ultimately prevent the availability of a known therapy for keratoconus to numerous young people in this country? The controversy over the FDA approval process for CXL was centered on the available data. Although there are many data on CXL, a critical look at these data should suggest that perhaps more consistent data using standardized protocols will help to

guide our practice patterns better regarding CXL and keratoconus, all with the ultimate goal to allow us to provide the best care for our patients with keratoconus.

Finally, beyond the data, the issue of availability of this technology for all who would benefit also will depend on cost. Now that FDA approval has been established, how will the varying protocols affect coverage by insurance companies? Because CXL ultimately should decrease the number of corneal transplants required, insurance companies should take a serious look at the cost-to-benefit ratio in covering the procedure. Physicians also have a responsibility to lead the reimbursement issue: if CXL really works and will prevent patients from needing corneal transplants, wouldn't keeping this out of reach for all who need it be akin to taking aspirin out of reach for all who are at risk for cerebrovascular events? Our ophthalmology community will need to set the ethical bar and to establish practice patterns that will demand fair and cost-effective availability of this technology for all who would benefit.

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