The Evolution of Corneal Inlays

BY GEORGE O. WARING IV, MD; AND MARCONY R. SANTHIAGO, MD, PhD

Through the years, multiple procedures have been proposed for the surgical treatment of presbyopia, a ubiquitous disorder of the aging eye that affects more than 80 million emmetropic presbyopes in the United States alone.1 José I. Barraquer, MD, of Bogotá, Colombia, performed experiments with corneal implants as early as 1949.2 Since then, this refractive technology has undergone a series of improvements. The benefits of intrastromal corneal inlays for the treatment of presbyopia include potential reversibility, ease of implantation and reposi- tioning, and the potential to combine them with other refractive procedures to allow simultaneous correction of ametropias.

Challenges with early intrastromal corneal implants included corneal opacification, vascularization, keratolysis, and decentration.3-6 However, the development of materials with enhanced biocompatibility,7,8 advances in technology such as femtosecond lasers that facilitate the reliable creation of stromal pockets, and better understanding of physiology and wound-healing response have allowed significant maturation of this exciting technology.1-12

The mechanisms behind the current generation of inlays designed for the treatment of presbyopia can be divided into three categories: (1) small-aperture corneal inlays, (2) space-occupying inlays that create a hyperprolate cornea, and (3) refractive annular addition lenticules that work as bifocal optical inlays to create separate distance and near focal points (Figure 1).1

HISTORY
Early inlays were composed of flint glass and plexiglass for the correction of aphakia and high myopia.2 Peter Choyce, MD, of London, developed the use of PMMA and polysulfone inlays to treat Fuchs dystrophy and high myopia.5 High index polymers were an optically attractive material choice; however poor permeability limited their use. As a result, Barraquer developed human donor stromal lenticules for inlays (keratoaphakia) and onlays (epikeratoaphakia). Claes H. Dohlman, MD, of Boston, first described the use of a permeable lenticule in 1967.6 Hydrogel inlays were developed so as not to impede metabolic gradients across the stroma including nutrient flow to the anterior cornea. Although semipermeable hydrogel polymers allow free nutrient flow, they have a relatively low index of refraction and are therefore limited in optical power. Past inlay designs include the Kerato-Gel (Allergan, Inc., Irvine, California), which was designed for aphakia and composed of lidofilcon A. The Chiron inlay (Bausch + Lomb, Rochester, New York) was a meniscus hydrogel optical lens that ranged from 1.50 to 3.50 D in add power with a diameter ranging from 1.8 to 2.2 mm. The PermaVision Intracorneal Lens (Anamed, Lake Forest, California) was composed of a hydrogel-based material called Nutrapore with a water content of 78%. This lens, measuring 5.0 to 5.5 mm in diameter with a central thickness of 30 to 60 µm, intentionally altered surface curvature. This was followed by the IntraLens (now ReVision Optics, Inc., Lake Forest, California) in the evolution of space-occupying lenticules that intentionally altered surface curvature to create a multifocal cornea for the treatment of hyperopia and presbyopia. These technologies served as the precursor for the Vue+ inlay (formerly the PresbyLens, ReVision Optics, Inc.). The Intracorneal Microlens (BioVision AG, Brüggs, Switzerland) was a 3-mm diameter, 20-µm thick hydrogel annular add inlay with a central opening free of optical power that also allowed nutrient flow to the anterior central cornea. This inlay was designed for placement in a stromal pocket with a mechanical microkeratome pocket maker. The Microlens went on to be known as the InVue, the precursor to the Flexivue inlay (Presbia, Amsterdam, Netherlands).

CORNEAL PHYSIOLOGY AND INLAYS
The physiologic process of wound healing has been described as a complex cascading sequence of events...
that normally contribute to wound repair and reestablish normal corneal physiology.13 One goal of successful inlay implantation is to respect the precise organization of corneal structure, a major factor in corneal transparency.14-16 Corneal stromal fibrils have a characteristically narrow diameter and are aligned in parallel arrays and immersed in specialized clusters of proteoglycans.17-20 The corneal stroma undergoes homeostatic remodeling via the functions performed by keratocytes and possibly other cell types, including bone-marrow-derived cells and myofibroblasts. Keratocytes are responsible for production and maintenance of the extracellular matrix of the corneal stroma.21 Changes in environmental conditions, such as an intrastromal implant, may modulate kerocyte phenotype, resulting in functional changes in gene expression, contractility, matrix production, and other characteristics that contribute to the wound-healing response. Therefore, the goal of successful inlay design, implantation technique, and perioperative care is to minimize or eliminate these potential changes.

The absence of vasculature in the cornea implies that nutrients must diffuse through its boundaries, and therefore the diffusivity of the inlay affects the way nutrients are transported through the cornea. Oxygen transport is normally not altered as much as glucose transport because the solute can diffuse from both anterior and posterior surfaces.22-25

Inlays should be semipermeable, allowing oxygen supplied from the tear film and glucose supplied from the aqueous humor to nourish the vital corneal cells and enabling catabolic products to be delivered to the aqueous humor. This mechanism is essential to prevent anterior stromal necrosis and corneal edema.22,26,27

Santhiago et al28 recently showed that the Kamra corneal inlay (AcuFocus, Inc., Irvine, California) appeared to have no deleterious effects on corneal epithelial or stromal tissues 6 weeks after surgical insertion in an animal trial. These results suggest that the Kamra corneal inlay may be effective in maintaining the normal nutrient flow to the anterior stroma. In preclinical studies, hydrogel inlays have also been shown to be well tolerated in animal trials.1,27

**MECHANISM OF ACTION**

**Small-aperture inlay.** The Kamra inlay is based on the concept of small-aperture optics, in which light rays pass through a small aperture and thereby increase the eye’s depth of focus. Thus, this technology uses the principle of the pinhole effect to increase depth of field and minimize the effects of refractive error. Clinical studies published to date have demonstrated that the Kamra inlay (ACI 7000) effectively improved near vision and reading speed in patients with presbyopia.9-12 Stability has been demonstrated up to 5 years after implantation. Small-aperture technology is resilient against the progressive nature of presbyopia, a unique feature among corneal-based presbyopic surgical solutions.

**Space-occupying inlay to create a hyperprolate cornea.** The Vue+ corneal inlay was developed in 2007 as the PresbyLens and was marketed for the treatment of plano presbyopia. The Vue+ is a permeable hydrogel lenticule that allows fluid and nutrient transmissiion. Recent design changes include enlarging the diameter from 1.5 mm to 2.0 mm, which expands the...
near optical zone and improves useful near vision. The lenticle is approximately 10 µm thick at the periphery and ranges from 24 to 40 µm in thickness at the center. The proprietary hydrogel-based material has a water content and a refractive index similar to those of the human cornea. The inlay is inserted either under a LASIK flap or into a corneal pocket at a depth of approximately 120 to 130 µm in the nondominant eye. The lenticle improves near and intermediate vision by inducing a differential surface curvature change, resulting in a multifocal cornea.1

Refractive annular add lenticle. The Flexivue MicroLens is the only intrastromal corneal inlay in development that utilizes refractive add power. The Flexivue is composed of a hydrophilic acrylic polymer, measuring 3 mm in diameter with an edge thickness of 20 µm. This bifocal optical inlay has separate distance and near focal points. The central zone is free of refractive power, and the peripheral zone has a standard refractive power with an index of refraction higher than that of the cornea, generating 1.25 to 3.00 D of add power. The Flexivue is inserted into a stromal pocket with an insertion device in the nondominant eye, concentric with the estimated line of sight.1

CONCLUSION
Intrastromal corneal inlays appear to be safe and effective options for the surgical management of presbyopia. A unique benefit of this emerging technology is that inlays are removable. Further studies are still needed to confirm long-term safety and to investigate different applications such as after refractive procedures, including in pseudophakic, laser vision correction, and thermal keratoplasty approaches.

George O. Waring IV, MD, is a subspecialist in corneal refractive and intraocular lens surgery at ReVision Advanced Laser Eye Center in Columbus, Ohio, and Medical Director, Division of Ophthalmology, for St. Joseph’s Translational Research Center in Atlanta, Georgia. Dr. Waring states that he is the world surgical monitor for AcuFocus. He may be reached at email: georgewaringiv@gmail.com.

Marcy R. Santhiago, MD, PhD, is a second-year postdoctoral fellow in refractive surgery at the Cleveland Clinic Foundation in Cleveland, Ohio. He states that he has no financial interests to disclose. Dr. Santhiago may be reached at email: marconysanthiago@hotmail.com.

TAKE-HOME MESSAGE
- The benefits of intrastromal corneal inlays include potential reversibility, ease of implantation, and the potential to combine them with other refractive procedures.
- One goal of successful inlay implantation is to respect the precise organization of the corneal structure.
- Clinical evidence suggests that corneal inlays are safe and effective options for the surgical management of presbyopia.

REFERENCES

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