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Excimer Laser Shaped Allograft Corneal Inlays for Presbyopia: Initial Clinical Results of a Pilot Study

Aylin Kılıç[1*], **Burcu Nurözler Tabakcı**[1], **Merve Özbek**[2], **David Muller**[3] **and Michael Mrochen**[3,4]

[1]*Istanbul Medipol University School of Medicine, Ophthalmology Department, Istanbul,Turkey*

[2]*University of Health Sciences, Van Training and Research Hospital, Ophthalmology Clinic, Van, Turkey*

[3]*Allotex Inc. Boston, USA & Allotex GmbH, Zurich, Switzerland*

[4]*Swiss Eye Research Foundation, Rheinach, Switzerland*

[*]**Corresponding author:** Aylin Kılıç, Department of Ophthalmology, Istanbul Medipol University School of Medicine, Istanbul, Turkey; E-mail: aylinkilicdr@gmail.com

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Abstract

Purpose: To evaluate the clinical feasibility of precision shaped lenticules comprised of sterile allograft corneal tissue designed to optimize the shape of the anterior corneal surface for presbyopia correction by increasing the depth of focus and central corneal power within a prospective pilot study.

Methods: This case series included 12 eyes of 12 patients with a follow-up of 6 months. Corneal lenticules with a refractive target add power of 2.5 D (Transform, Allotex Inc. Boston, USA) is implanted in the non-dominant eyes. Manifest, and cycloplegic refraction, uncorrected distance visual acuity (UCDVA), uncorrected near visual acuity (UCNVA), best corrected distance visual acuity (BCDVA),best corrected near visual acuity (BCNVA) were measured preoperatively and 6 months postoperatively.

Results: The mean preoperative UCNVA (logMAR) in the treatment eye was 0.52 ± 0.14 and was significantly increased to 0.10 ± 0.06 (p=0.000) at the 3 month follow-up. All eyes had a UCNVA of 0.20 or better at the last follow-up visit. An expected myopic shift of the preoperative spherical equivalent refraction of +0.25 ± 0.29 D to -0.11 ± 0.28 D (p=0.017) was found. Nine out of the 12 patients reported that they were satisfied or very satisfied with the outcome of the procedure and adapted towards the blended vision generated by the increase of depth-of-focus in the non-dominant eye.

Conclusion: Preliminary results of this pilot study indicate that the sterile allograft lenticules enhance the visual performance of the patient for the near vision needs. Larger clinical studies are needed to demonstrate the effectiveness and safety with long term follow-up.

Keywords: Presbyopi; Allograft Corneal Inlay; Refraction; Near Vision

Introduction

Corneal inlays provide the refractive surgeon a method to provide patients near/or surgical vision correction option to correct presbyopia without the risk associated with intraocular surgery. One general advantage of corneal inlays compared to laser ablation procedures is that they are additive and do not actually remove tissue for the optical correction. The capacity for removal or future options of any other type of presbyopia correction is preserved [1]. In recent years, non-allogeneic synthetic cornea implants have been used for this purpose and good visual and refractive outcomes have been obtained [2,3].

Although synthetic implants are made of biocompatible materials they are not equivalent to an allogeneic implant in terms of biocompatibility. There are 3 types of synthetic corneal inlays for presbyopia discussed in recent publication with various stages of development and commercial release. These inlays add refractive power to the central cornea by implanting a refractive addition of +1.5 to +3.5 diopters (D) (Flexivue Microlens, Presbia Cooperatief U.A), enhance near and intermediate vision (Raindrop Near Vision Inlay, Revision optics, Inc.), or use small-aperture optics to increase the depth of focus (Kamra corneal inlay, Acufocus, Inc) [4-6].

The development and introduction of the synthetic corneal inlays for the treatment of presbyopia is still associated with changes in the natural metabolic functions of the human cornea and serious adverse events have been reported [7-10].

Changing the refractive properties of the eye by using natural corneal tissue was initially introduced by Barraquer in 1949 [11]. Since its introduction by Kaufman in 1980, thousands of patients have undergone epikeratophakia [12]. This inlay procedure named epikeratophakia consists of an implantation of a refractive lenticule onto Bowman's layer and under the epithelium. In the 1980's, this procedure was performed regularly in hyperopic, myopic and aphakic eye but unpredictable refractive results and difficulty of the preparing and storage of the refractive lenticules limited the use of this technique [13].

However, the surgical procedure of epikeratophakia was frequently associated with a shallow groove is produced by a trephine in the stroma and the donor graft is sutured into place with radial tight sutures to reform the cornea after the recipient epithelium has been scraped away. In contrary, corneal inlays implanted under a standard

lasik flap do not require suturing and offer the potential for removal or exchange with different ass power, if required.

The possibility to remove or exchange is also a benefit when comparing the corneal inlays with the ability of performing presbyopia excimer laser surgeries [14]. In addition, the principles of mono-vision in laser refractive surgery or clear lens extractions are associated with limitations.

Whitman et al. noted that not all patients tolerate mono-vision well, and the limit of refractive disparity is approximately 1.5 D, less than the full 2 to 3 D range needed for best near vision function [15]. Mono-vision has the negative side effects of reduced distance visual acuity, reduced stereopsis, reduced contrast sensitivity, and reduced quality of vision [16].

Clear lens extraction and replacement with a multifocal IOL carries surgical risks including retinal detachment, macular edema, biometric errors, photopic phenomena, reduced contrast sensitivity, loss of best corrected visual acuity, visual disturbances, patient dissatisfaction, and importantly, the procedure is not reversible [15]. Therefore, corneal inlays that are designed to increase the depth of field in the non-dominant each eye and achieve good binocular vision at all distances are proposed to be a compromise for presbyopic patients.

The purpose of this prospective pilot study was to evaluate the clinical feasibility of precision shaped lenticules comprised of sterile allograft corneal tissue designed to optimize the shape of the anterior corneal surface for presbyopia correction by increasing the central corneal power to provide increase in depth of focus in the non-dominant eye to improve near visual acuity in emmetropic presbyopic patients.

Method

This case is a series of 12 eyes of 12 patients that underwent implantation of a presbyopia allograft corneal inlay. Approval was obtained by the Institutional Review Board (IRB)/Ethics Committee of the Istanbul Medipol University (Approval number 08). Subjects were only enrolled after educating them on the procedure and the purpose of the procedure, the purpose of the intervention and a signed informed consent was obtained to volunteer in the clinical trial according to the tenets of the Declaration of Helsinki.

Clinical examinations included the medical and ophthalmic history , Tear break –up time (TBUT) and Schirmer tests, the patients were examined preoperatively, and then at 1 week, 1 month, and 6 months postoperatively, as well as preoperative and postoperative measurements such as manifest and cycloplegic refraction, uncorrected distance visual acuity (UCDVA), uncorrected near visual acuity (UCNVA), best corrected distance visual acuity (BCDVA),best corrected near visual acuity (BCNVA), and slit-lamp examination, fundus examination.

All visual acuity data are represented in logMAR units. Objective clinical measurements included corneal tomography and topography (Pentacam, Oculus, Germany), ocular wave front aberrometry (iDesign, AMO, Santa Ana, CA, USA), and anterior segment OCT (Spectralis, Heidelberg instruments Germany).

To determine ocular dominance motor dominant eye tests were performed twice preoperatively at the first examination and immediately before surgery. The person, with both eyes open, to look through an aperture with extended hands and visualize a distant object through the hole.

Inclusion criteria were stable vision (i.e. manifest and/or cycloplegic refraction spherical equivalent (MRSE) within 0.50 D over the prior 12 months in the treatment eye) and in the non-dominant eye a MRSE between -0.75 and +1.00 D with refractive cylinder of less than 0.75 D.

Contact lens wearers who participated in this case series study had to discontinued hard or rigid gas permeable lenses for at least 3 weeks and discontinued soft lenses for at least 1 week prior to the baseline examination. The inclusion criteria for the refraction was choosing to assure the effectiveness of the inlay for near vision add of 2.5 D at 40 to 50 cm. The production process includes a final metrology testing of the lenticule shape within the paging by means of the optıcal coherence tomography with an acceptance range of ± 0.5 D for the near vision add.

The exclusion criteria included any ocular or uncontrolled eyelid disease, corneal abnormality (including endothelial dystrophy, recurrent corneal erosion, etc.), glaucoma, glaucoma suspect, anterior segment pathology, significant cataract, history of herpes zoster or herpes simplex keratitis in the treatment eye, topographic signs of keratoconus (or keratoconus suspect) or other ectatic disorders in either eye, distorted or unclear corneal mires on topography maps of the treatment eye, using systemic medications with significant ocular side effects or pregnancy. Eyes that had corneal thickness of 500 μm or thinner and dry eye were not included in the study.

All eyes were implanted with corneal lenticules at an intended refractive add power of 2.5D (Transform, Allotex Inc. Boston, USA) was performed by the same surgeon (AK) after the non-dominant eye was prepared for surgery. All TransForm Inlay used in this case series were proposed and formed by the manufacturer (Allotex Inc. Boston USA). In brief, the lenticules comprised of sterile, allogeneic corneal tissue designed to alter the shape of the anterior surface of the cornea, thereby adjusting the point of focus on the retina.

The tissue derives from human corneas, procured under strict ethical standards from an Eye Bank Association of America (EBAA) and each donor cornea was cleared for human use by the approved eye bank for lamellar procedures (Lions Vision Gift, Portland, OR, USA). After receipt and inspection of the tissue by the manufacturer, the processing consists of trephining the cornea into 3 buttons of 3 millimeters in diameter with an appropriately sized biopsy punch, and then slicing the buttons, along the lamellar plane, using a customized microkeratome (Allotex Inc. Boston USA) to produce corneal blanks of a nominal thickness (thickness approximately 25-40 microns).

These corneal blanks are then placed into an environmentally controlled chamber to undergo excimer laser (Allotex, production laser, wavelength 193 nm; 3D Micromac, Chemitz, Germany) processing to form the desired shape and size lenticules. All steps involving shape formation and changes of shape are monitored by customized high resolution optical coherence tomography (OCT 1300 nm, Thorlabs, Munich, Germany) to insure that the lenticules are accurately shaped. The formed lenticules are packaged and stored in recombinant albumin solution and then undergo an e-beam sterilization process.

The corneal tissue used in our case series was fully screened according FDA regulations before the tissue was processed for lenticule preparation. All corneas used for tissue processes were considered to safe for corneal transplantation, but not suitable for fresh tissue

transplantation (e.g. penetrating keratoplasty, DMEK, DSAEK) mainly due to low numbers of endothelium cell count or other processual reasons. After processing the tissue, all corneal lenticules were sterilized by means of a validated ebeam sterilization process allowing storage and shipment of the tissue under room temperature conditions. Based on this processing of the tissue, we do consider the sterile allograft corneal inlays as risk mitigated for any disease transfer.

The TransForm Inlay is designed to be placed directly on top the recipient's stroma that has been exposed by the creation of a femtosecond laser-created flap. The final shape, after laser sculpting, is 3 mm in diameter with a central thickness of approximately 20 microns. The optical principle of the presbyopia Inlay is the increase of depth-of-focus based on the introduction of optical aberrations or in other words the increase of corneal asphericity leading to an increase of subjective and objective depth-of-focus (DOF) or depth-of-field with increasing spherical aberrations [17-21].

More specifically, a combination of primary (Z40) and secondary (Z60) spherical aberrations of opposite signs yield the highest increase in DoF. At the same time, one has to consider in the design a decrease in visual acuity with increasing amounts of induced spherical aberrations. Yi et al. reported an increase of 0.31 logMaR/µm of zernike coefficient Z40, 0.83 logMaR/µm of Z60 and -0.40 logMaR/µm of the combination of Z60+Z40 21.

Thus, the design of the corneal inlay compromised an increase of depth of focus with an intended add power of +2.5 D and a loss of distance visual acuity of less the one line in the non-dominant eye. As second consequence arising from the optical design of increasing mainly rotational symmetric higher order aberrations to increase in DOF is a myopic shift in the defocus of the optical system of the eye need of approximately -0.5 D (pupil size 5 mm).

The simulated optical effect of the presbyopia lenticule inducing defocus, spherical aberrations (4th and 6th Zernike order) are shown by image simulation (Figure 1). Here, through focus retinal image for a +2.5 D refractive add was simulated by the modulation transfer function of the spherical aberrations and an image of a snellen letter E.

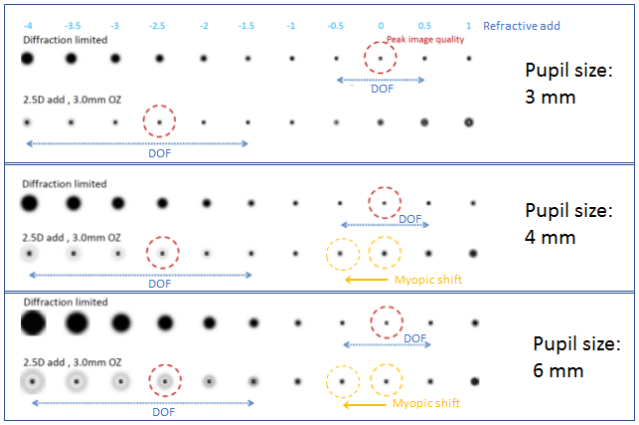

Figure 1: The simulated optical effect of the presbyopia lenticule inducing defocus, spherical aberrations (4th and 6th Zernike order).

Through focus retinal image quality for a +2.5 refractive add with an optical zone of 3 mm for three different pupil diameters (3 mm, 4 mm and 5 mm). Convolved Images are derived from the modulation transfer function of the optical design and Snellen E visual acuity letter at different refractive adds (0 D to -4 D). Diffraction limited represents the case without lenticule compared to the retinal image quality with presbyopia-correcting lenticules. The blue arrows represent the estimated range of depth-of-focus (DOF) and the red dashed circles indicate best image quality of letter E.

The yellow circles represent the image quality for far distance vision with the lenticule. A potential myopic shift of -0.5 D can be noted due to the introduction of spherical aberration. This is due to positive defocus induced by the corneal shape change in addition to the interaction of defocus with primary spherical aberration to optimize retinal image quality with larger pupil sizes. Besides this, a slight reduction in monocular distance vision can be noted for the benefit of increased depth-of-focus. For biocular vision, the somuation of both cases (with and without lenticule) can be considered as the implantation is only performed in the non-dominant eye of nearly emetropic patients.

As a first surgical step, a femtosecond assisted flap was created (iFS 150kH, Intralase, Abbott Medical Optics, Santa Ana, CA, USA) with an intended flap thickness of 110 microns, a flap diameter of 8.8 mm and a superior hinge of 80 degrees. The stromal interface was rinsed carefully with BSS during and after opening of the flap. As a second surgical step, the corneal inlay was carefully transferred onto the exposed stromal bed by means of a loop like instrument (inner diameter 3 mm) and centered on the cornea towards the pupil center of the patient eye (Figure 2) under a surgical microscope of a clinical excimer laser (Visix S4, CustomVue S4IR Abbott Medical Optics Inc., Santa Ana, CA, USA).

During the final surgical step, the surgeon assured smoothness of the lenticules edges and checked the roundness of the lenticule prior to the replacement of the flap by means of a 25 G, 25 mm, 12 mm angled tip cannula. A soft bondage contact lens (ACUVUE Oasys, Johnson & Johnson Vision Care Inc.) was placed onto the cornea after the flap was reposition onto the stromal bed.

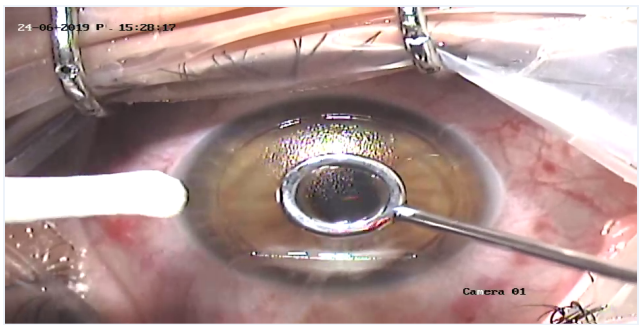

Figure 2: The corneal inlay was transferred onto stromal bed by means of a loop like instrument (inner diameter 3 mm) and centered on the cornea towards the pupil center.

The postoperative topical medication regimens were identical for each eye, which was 0.3% levofloxacin five times a day, 0.1% fluorometholone solution five times a day and a preservative-free tear supplement eight times a day for 1 month. The follow-up regime was 1 day, 1 week, 1 and 3 months postoperatively. All patients were evaluated carefully about dry eye symptoms postoperatively. We evaluated for the signs of dry eye syndrome, including conjunctival

injection, punctate keratitis, reduced tear meniscus, tear film debris, abnormal TBUT routinely in each visit.

Our patients were older than the patients that underwent routine LASIK operations. We attached importance of dry eye development. Therefore the patients were treated with preservative-free artificial tears intensively describe and we placed in each patient absorbable, 2 mm length, collagen punctal plugs (Soft Plug, Extended Duration Plug By Oasis) for occlusion of the lacrimal drainage system and conserving tears.

As primary outcome measures of this case series, we compared pre and postoperative best corrected visual acuity to evaluate the safety of the procedure at 3 months. To evaluate the effectiveness of the presbyopia implant we compared preoperative uncorrected near visual acuity to postoperative results at the 3 month follow-up. All visual acuity data were analyzed by changes in lines and statistical comparison was done by means of a two-sited paired t-test. SPSS software (Statistical Package for Social Sciences, version 20, SPSS Inc., Chicago, IL, USA). Slit map investigation (lamp examination) were performed at all follow-up visits to observe the corneal healing response as well as possible adverse or serious adverse events.

Objective measurements to evaluate the refractive power add achieved with the corneal inlays were performed by analyzing the central 3 mm of topography data and by comparing the change in 3rd to 6th Zernike order aberration at a pupil size of 5 mm. The statistical comparison of the pre and postoperative objective data were again performed by means of a two-sited paired t-test. Anterior segment OCT was performed with the intention to measure the change in corneal thickness and to derive the thickness of the implanted lenticule.

Results

The mean age of the 12 patients included in this case series was 52 ± 3.2 years (range 46 to 57 years). Two patients (16.7%) were female, and ten (83.3%) were male. Of the twelve inlay non-dominant eyes, seven (58.3%) were left eyes and five (41.6%) were right eyes. Table 1 gives the preoperative and postoperative parameters for the inlay eyes.

	Preoperative Mean ± SD	Postoperative Mean ± SD	p
UCDVA	0.05 ± 0.06	0.06 ± 0.04	0.754
BCDVA	0.00 ± 0.00	0.05 ± 0.05	0.007
UCNVA	0.52 ± 0.14	0.10 ± 0.06	0
Corneal Thickness	554 ± 45	553 ± 46	0.913
SE	+0.25 ± 0.29	-0.11 ± 0.28	0.017

Table 1: The mean preoperative BCVA (logMAR) of 0.00 ± 0.00 was changed to 0.05 ± 0.05 (p=0.007) at the three month follow-up. A total of 7 eyes lost 0.1 logMAR of BVCA.

The mean preoperative UCNVA in the treatment eye was 0.52 ± 0.14 was increased to 0.10 ± 0.06 (p=0.000) the 6 month follow-up. On average the UCNVA increased by 5 ± 1.88 lines compared to the preoperative examination. All eyes had a UCNVA of 0.63 logMAR or better at the last follow-up visit.

The mean preoperative UCDVA of 0.05 ± 0.06 was remained unchanged when compared to the 3-months postoperative UCDVA of 0.06 ± 0.04 (p=0.75). A total of 8 eyes remained unchanged and 2 eyes lost one line, 2 eyes lost 2 lines and none of the eyes lost more than 3 lines of UCDVA. Preoperative and postoperative binocular UCDVA remained unchanged.

An expected myopic shift of the preoperative spherical equivalent refraction of +0.25 ± 0.29D to -0.11 ± 0.28D (p=0.017) was found. The preoperative manifest cylinder of -0.04 ± 0.15 was remained unchanged to -0.06 ± 0.16 D postoperatively.

All surgical interventions were uneventful and the postoperative slit lamp examination at the first day showed only a slight edema within the flap. Three months after a successful inlay implantation the corneas clear and the inlay is almost imperceptible (Figure 3).

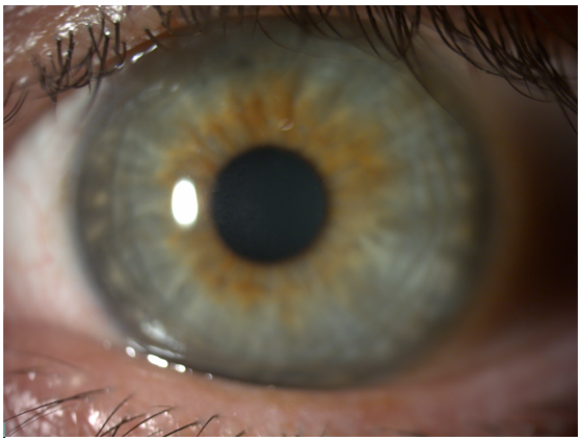

Figure 3: Six months after the corneas were clear and the inlay was almost imperceptible.

Topography measurement showed a central steeping of 2.25 D (± 0.5) within the inner 3 mm of the cornea. An example of the change of the anterior corneal surface is provided (Figure 4). The difference map demonstrates the increase in corneal power over the center of the pupil. All implanted lenticules were found to be acceptable centered within ± 0.3 mm at the 6 month follow-up.

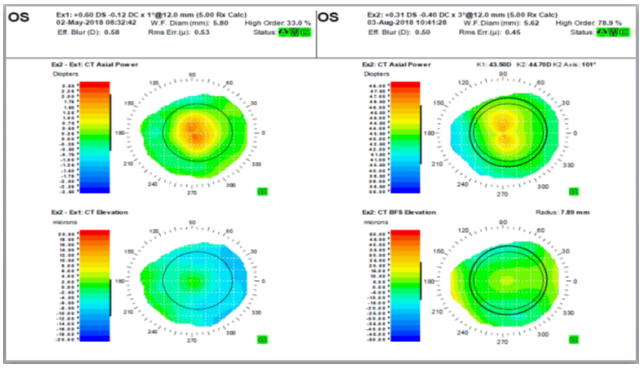

Figure 4: Change in corneal topography after implantation is provided.

The Scheimpflug measurement were sound to be variable compared to the reflection based corneal topography from the iDesign device. The central corneal thickness were also found to be 554 ± 45 microns preoperatively and 553 ± 46 microns postoperatively (p=0.913).

The ocular wave front aberrometry demonstrated an increase in 4th and 6th Zernike order spherical aberration at a 5 mm pupil. The mean increase of 4th order aberration was -0.166 ± 0.10 (p=0.003) microns and +0.025 ± 0.03 (p=0.0495) for the 6th order spherical aberration. An example for the change in total and higher order aberrations is shown (Figure 5).

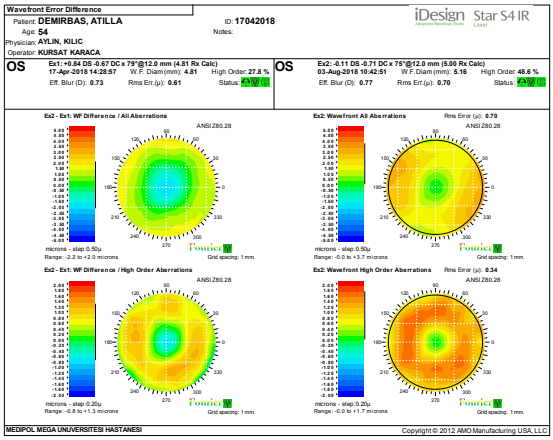

Figure 5: Change in total and higher order aberrations.

Grade 1 mild faint reticular corneal haze was found in two patients and disappeared after 6 months. Nine out of the 12 patients reported that they were satisfied or very satisfied with the outcome of the procedure and adapted towards the blended vision generated by the increase of depth-of-focus in the non-dominant eye, one patient reported to be moderately satisfied due to dry eye symptoms and an induced corneal astigmatism of -0.75 D.

Discussion

The purpose of this initial clinical evaluation was to demonstrate clinical feasibility of sterile, allograft lenticules as an inlay for presbyopia. The clinical results of this small case series have demonstrated a significant increase in UCNVA in the non-dominant eye. The increase of the depth of focus driven by a controlled increase 4^{th} and 6^{th} Zernike spherical aberration results in an average central corneal power add of 2.25D and a slight myopic shift of approximately -0.5D.

The results of the non-dominant eyes show that the implantation of the presbyopia lenticule is associated with a small loss of uncorrected distance vision acuity associated with the myopic shift and a small loss of approximately one line in BCDVA due to the intended increase in spherical aberration. Intra-operative and postoperative observations demonstrated that the implantation of a sterile allograft is not associated with adverse or serious adverse events and none of the eyes had a safety concerning loss of BCDVA.

These initial clinical results of the sterile allograft inlays are comparable to the reported outcomes of the hydrogel corneal inlay (Raindrop, Revision Optics, Inc, Lake Forest, CA) and a small aperture corneal inlay (KAMRA, Acufocus, Inc, Irvine, CA). The hydrogel corneal inlay also steepens the anterior corneal curvature increasing the optical power of the eye to provide vision correction of +1.50 D to +2.50 D of reading adds. The opaque annulus inlay increases depth of focus in the implanted eye by reducing the pupil size to provide a +1.00 D to +2.50 D of reading add.

The primary effectiveness endpoint in the study for the hydrogel inlay was met with 92% of eyes at 24 months having an uncorrected near visual acuity of 20/40 or better. At 1 week, the mean UCNVA was 20/25 (+0.10 ± 0.13 logMAR), and the mean UCNVA exceeded 20/20 from 3 months onward (+0.02 ± 0.10 logMAR at 3 months and +0.03 ± 0.10 logMAR at 12 months). By 3 months, 93% of the population achieved 20/25 UCNVA in the treated eye. At 1 year in the treated eye, on average, UCNVA improved by 5.1 lines, uncorrected intermediate visual acuity (UCIVA) improved by 2.5 lines, and uncorrected distance visual acuity (UCDVA) decreased by 1.2 lines. From 3 months through 1 year, 93% of subjects achieved UNVA of 20/25 or better 15.

The primary effectiveness endpoint for the opaque corneal inlay was met with 83.5% of eyes at 12 months having an uncorrected near visual acuity of 20/40 or better. At 3 month follow-up, 92% (11/12) of patients had a Mono UCNVA of 20/40 (J5) or better, with 75% (9/12) seeing 20/25 (J2) or better [22].

Our results with the sterile allograft inlays are comparable to the gain in UCNVA with 92 % and 83.5% of 20/40 or better reported for the hydrogel and the opaque inlays [15,22].

For the hydrogel inlays in the FDA trial the most common adverse events were ocular infection (2%), epithelial ingrowth (3%), loss of best corrected distance visual acuity >2 lines (3%), increase in IOP>10 mmHg (2%), diffuse lamellar keratitis (2%) and secondary surgical interventions including 5% of inlays being exchanged and 7% of inlays being explanted. For the opaque corneal inlays in the FDA trial the overall cumulative ocular adverse event rate was 16.7% with the most common adverse events being secondary surgical interventions including 8.7% of inlays being removed, decreased vision of >2 lines in 5.9% of eyes, increased intraocular pressure in 3.3% of eyes and diffuse lamellar keratitis in 1.2%. We did not observe such adverse events in the small case series reported here, however, this might be due to the small sample size of our feasibility case series.

Nevertheless, hydrogel corneal inlays can affect the oxygen and nutrients flow through the patient's cornea with a possibility to affect the metabolism of the cornea 10. In contrast, sterile allograft corneal inlays may offer safety advantages over artificial corneal inlays (e.g. hydrogel material) for presbyopia due to it's biologically compatibility [23].

A very recent development is the use of corneal lenticules as intra-stromal implants. Autologous lenticules obtained using the small incision lenticule extraction (SMILE) procedure was implanted for treatment of hyperopia, presbyopia and keratoconus. Four emmetropic presbyopic patients underwent PrEsbyopic Allogeneic Refractive Lenticule (PEARL) corneal inlay implantation their non-dominant eye. UCNVA improved from J8 to J2 in one and from J5, J6, and J7, respectively, to J2 in three operated eyes with improvement between three and five lines in all eyes during 6 months follow-up period.

Unlike the synthetic implants, there is unhindered passage of oxygen and nutrients because the PEARL inlay is made of allogeneic cornea, thus ensuring stable corneal conditions and decreasing the risk for corneal necrosis and melt. The use of allogeneic tissue provides biocompatibility and good integration into the cornea, thus avoiding problems such as inflammation related to insertion of synthetic material into the cornea [24].

Pradhan et al. [25] described endokeratophakia in which a SMILE lenticule from a myopic patient is implanted into a recipient eye through a small incision to correct hyperopia. After 1 year, the spherical equivalent refraction reduced by 5.25 D from +11.25 D to +6.00 D and the mean keratometry increased by 1.81 D from 41.39 D to 43.20 D. In this case, the implanted lenticule caused the cornea to bulge both anteriorly and posteriorly.

The result of posterior surface changes and epithelial thickness remodeling was under correction of hyperopia. Consequently, we decided to perform the implantation of the presbyopia lentıcules under a standard Lasik flap to minimize possible biomechanical influence on the intended correction.

Our initial clinical results do not provide long term data in relation to effectiveness and safety. However, the long term results reported on epikeratophakia of up to 30 years might provide a good indication on the survival of the implant. Kurmeich summarized the long term outcomes of epikeratophakia and found that all lenticules remained stable during the 10 year follow-up. Postoperative astigmatism was ≤ 3.25 diopters and the spherical equivalent remained almost stable after 1 month. Neither rejection nor lenticule opacification was observed over the entire follow-up [26].

Since the corneal allograft is acellular, sterile tissue donor immunogenicity will be reduced 23. The procedure is easily reversible with the allograft being removed in a minimally invasive procedure [27]. A limitation of epikeratophakia was the accuracy of shaping the tissue and accurately measuring the lenticule shape. The lenticules used in this report we shaped by means of a customized industrial excimer laser and measured by optical coherence tomography for validating the shape.

Placido disk corneal topography is the gold standard procedure to detect and diagnose corneal aberrations (i.e., keratoconus), analyze pre- and postoperative results of refractive surgery. Scheimpflug camera provides a wider range of scale colors and, in some cases; this may be problematic, because the topography may not show relevant details. Placido disc is established as a valid and reliable method of corneal evaluation, and its use has become part of routine clinical practice [28,29].

Conclusion

In conclusion, sterile allograft lenticules were implanted under a femtosecond laser created corneal flap to enhance the visual performance of the patient with a material that is biocompatible and precisely shaped for the individual's near vision needs. The results of this prospective pilot study were found to be comparable to previously published hydrogel and small aperture corneal inlays. Therefore, the sterile allograft corneal inlays can be considered to be suitable for a larger prospect clinical study to demonstrate the effectiveness and safety with long term follow-up.

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Financial Interest

David Muller and Michael Mrochen are employees and shareholders of Allotex Inc. and Allotex GmbH.

References

1. Lindstrom RL, Macrae SM, Pepose JS, Hoopes PC (2013) Corneal Inlays for Presbiyopia Correction. Curr Opin Ophthalmol 24: 281-287.
2. Tomita M, Huseynova T (2014) Evaluating the short-term results of KAMRA inlay implantation using real-time optical coherence tomography-guided femtosecond laser technology. J Refract Surg 30: 326-329.
3. Vukich JA, Durrie DS, Pepose JS, Thompson V, van de Pol C, et al. (2018) Evaluation of the small-aperture intracorneal inlay: Three-year results from the cohort of the U.S. Food and Drug Administration clinical trial. J Cataract Refract Surg 44: 541-556.
4. Bouzoukis DI, Kymionis GD, Limnopoulou AN, Panagopoulou IS, Pallikaris IG, et al. (2013) Visual outcomes and safety of a refractive corneal inlay for presbiyopia using femtosecond laser. J Refract Surg 29: 12-28.
5. Garza EB, Gomez S, Chayet A, Dishler J (2013) One-year safety and efficacy results of hydrogel inlay to improve near vision in patients with emmetropic presbiyopia. J Refract Surg 29: 166-172.
6. Seyeddain O, Hohensinn M, Riha W, Nix G, RückL T, et al. (2012) Small-aperture corneal inlay for the correction of presbiyopia: 3-year follow-up. J Cataract Refract Surg 38: 35-45.
7. Moarefi MA, Bafna S, Wiley W (2017) A Rewiev of Presbiyopia Treatment with Corneal Inlays. Ophthalmol Ther 6: 55-65.
8. Duignan ES, Farrell S, Treacy MP, Fulcher T, O'Brien P, et al (2016) Corneal inlay implantation complicated by infectious keratitis. Br J Ophthalmol 100: 269-273.
9. Dexl AK, Jell G, Strohmaier C, Seyeddain O, Riha W, et al (2015) Long-term outcomes after monocular corneal inlay implantation for the surgical compensation of presbyopia. J Cataract Refract Surg 41: 566-575.
10. Mulet ME, Alio JL, Knorz MC (2009) Hydrogel intracorneal inlays for the correction of hyperopia: outcomes and complications after 5 years of follow-up. Ophthalmology 116: 1455-1460.
11. Barraquer JI (1996) The history and evolution of keratomileusis. Int Ophthalmol Clin 36: 1-7.
12. Kauffman HE (1980) The correction of aphakia. XXXVI Edward Jackson Memorial Lecture. Am J Ophthalmol 89: 1-10.
13. Werblin TP, Blaydes JE (1983) Epikeratophakia: existing limitations and future modifications. Aust J Ophthalmol 11: 201-207.
14. Vargas-Fragoso V, Alió JL (2017) Corneal compensation of presbyopia: PresbyLASIK: an updated review. Eye Vis (Lond) 4: 11.
15. Whitman J, Dougherty PJ, Parkhurst GD, Olkowski J, Slade SG, et al. (2016) Treatment of presbyopia in emmetropes using a shape-changing corneal inlay. Ophthalmology 123: 466-475.
16. Durrie DS (2006) The effect of different monovision contact lens powers on the visual function of emmetropic presbyopic patients. Trans Am Ophthalmol Soc 104: 366-401.
17. Benard Y, Lopez-Gil N, Legras R (2010) Subjective depth of field in presence of 4th-order and 6th-order Zernike spherical aberration using adaptive optics technology. J Cataract Refract Surg 36: 2129-2138.
18. Benard Y, Lopez-Gil N, Legras R (2011) Optimizing the subjective depth-of-focus with combinations of fourth- and sixth-order spherical aberration. Vision Res 51: 2471-2477.

19. Jansonius NM, Kooijman AC (1998) The effect of spherical and other aberrations upon the modulation transfer of the defocussed human eye. Ophthalmic Physiol Opt 18: 504-513.
20. Rocha KM, Vabre L, Chateau N, Krueger RR (2009) Expanding depth of focus by modifying higher-order aberrations induced by an adaptive optics visual simulator. J Cataract Refract Surg 35: 1885-1892.
21. Yi F, Iskander DR, Collins M (2011) Depth of focus and visual acuity with primary and secondary spherical aberration. Vision Res 51: 1648-1658.
22. Moshirfar M, Wallace RT, Skanchy DF, Desautels JD, Linn SH, et al. (2016) Short-term visual result after simultaneous photorefractive keratectomy and small-aperture cornea inlay implantation. Clin Ophthalmol 10: 2265-2270.
23. Utine CA, Tzu JH, Akpek EK (2011) Lamellar keratoplasty using gamma-irradiated corneal lenticules. Am J Ophthalmol 151: 170-174.
24. Jacob S, Kumar DA, Agarwal A, Agarwal A, Aravind R, et al. (2017) Preliminary Evidence of Successful Near Vision Enhancement With a New Technique: PrEsbyopic Allogenic Refractive Lenticule (PEARL) Corneal Inlay Using a SMILE Lenticule. J Refract Surg 33: 224-229.
25. Pradhan KR, Reinstein DZ, Carp GI, Archer TJ, Gobbe M, et al. (2013) Femtosecond Laser-Assisted Keyhole Endokeratophakia: Correction of Hyperopia by Implantation of an Allogeneic Lenticule Obtained by SMILE From a Myopic Donor. J Refract Surg 29: 777-782.
26. Krumeich JH, Daniel J, Knülle A (1998) Live-epikeratophakia for keratoconus. J Cataract Refract Surg 24: 456-463.
27. Greenbaum A, Kaiserman I, Avni I (2007) Long-term reversibility of epikeratophakia. Cornea 26: 1210-1212.
28. Rao SK, Padmanabhan P (2000) Understanding corneal topography. Curr Opin Ophthalmol 11: 248-259.
29. Guarnieri FA, Guarnieri JC (2002) Comparison of Placido-based, rasterstereography, and slit-scan corneal topography systems. J Refract Surg 18: 169-176.