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Long-Term Observations of the First Human Implantation of an Artificial Endothelial Layer for Endothelial Dysfunction: A Pilot Study

Hyeck-Soo Son, MD, Victor A. Augustin, MD,* Charles G. Eberhart, MD, PhD,† Maximilian Friedrich, MD,* Emanuel Reitemeyer, MD,* Nikola Henningsen, MD,* Oliver Hassel, MD,* Louise Blöck, MD,* and Gerd U. Auffarth, MD**

Purpose: To describe the long-term observations of the first human implantation of EndoArt, a synthetic endothelial implant, in a small cohort of patients with corneal edema secondary to endothelial dysfunction.

Methods: This retrospective case series analyzed 5 eyes from 5 patients who underwent EndoArt implantation, with a minimum follow-up of 12 months. Clinical outcomes, including corrected distance visual acuity and central corneal thickness, were evaluated pre- and postoperatively. Rebubbling procedures and any complications were recorded. Histological analysis was performed on 1 explanted corneal button.

Results: The mean follow-up was 38.4 ± 20 months (range: 19–72 months). A reduction in mean central corneal thickness was observed, from 741.2 ± 88.3 μm preoperatively to 558.4 ± 72.7 μm postoperatively ($P < 0.001$). Corrected distance visual acuity improved in 4 of 5 eyes, although not significantly overall ($P = 0.19$). The mean number of rebubbling procedures was 2.8 ± 1.3 per eye. No serious implant-related complications were observed during the follow-up period. Histological findings showed fibrocellular tissue partially integrating the implant, which may contribute to graft adherence. Two patients with Fuchs dystrophy received the device as a primary procedure because of ethical or religious constraints regarding donor tissue.

Conclusions: This small pilot series of the first human EndoArt implantation observed a significant reduction of corneal edema over time and a favorable safety profile in select patients. Although these findings are encouraging, they should be interpreted with caution given the limited sample size. Larger, controlled studies are needed to better understand the safety, efficacy, and long-term outcomes of this synthetic implant.

Key Words: corneal edema, Fuchs endothelial dystrophy, pseudophakic bullous keratopathy, endothelial dysfunction, EndoArt, artificial endothelial layer

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Today, endothelial keratoplasty (EK) such as Descemet membrane endothelial keratoplasty (DMEK) is the gold standard for treatment of endothelial diseases. Thanks to its good visual outcomes, fast visual recovery, favorable safety profile, and low rejection rate, DMEK has surpassed penetrating keratoplasty (PKP) to become the most common form of corneal transplant.[1–5]

Despite such clinical benefits, however, the global shortage of human donor tissues still limits timely access to DMEK in many countries.[6] Furthermore, the thin donor tissue with delicate endothelial cells makes the graft extremely vulnerable to intraoperative manipulations, which may affect its survival rate.[7] Postoperative complications such as immunological rejections may also cause graft failure.[8] Last, ocular comorbidities such as chronic glaucoma or previous surgeries such as implantation of glaucoma drainage devices may impair the long-term donor endothelial viability and undermine the surgical outcomes.[9,10] As a result, various novel therapeutic approaches have been introduced to overcome these challenges.

EndoArt (EyeYon Medical, Ness Ziona, Israel) is an artificial endothelial lamella that presents an alternative to DMEK. Composed of foldable, hydrophilic acrylic material that is dome-shaped to match the posterior corneal curvature, this water-impermeable implant is designed to impede stromal imbibition of the aqueous humor into the central cornea, thereby reducing its thickness in eyes with corneal

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From the *Department of Ophthalmology, University of Heidelberg, Heidelberg, Baden-Wuerttemberg, Germany; and †Division of Ophthalmic Pathology, Wilmer Eye Institute, Johns Hopkins Medical Institutions, Baltimore, MD

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H.-S. Son and V. A. Augustin have contributed equally as shared first-authors.

Correspondence: Gerd U. Auffarth, MD, FEBO, FWCRS, David J. Apple International Laboratory for Ocular Pathology and International Vision Correction Research Centre (IVCRC), Department of Ophthalmology, University of Heidelberg INF 400, 69120 Heidelberg, Germany (e-mail: gerd.auffarth@med.uni-heidelberg.de).

edema. Since the first published in vivo description in 2021,[11] several studies reported their experiences with the synthetic lamella in diverse clinical scenarios.[12–21] However, there is a relative dearth of evidence on its long-term efficacy and safety.

Thus, in this study, we report our long-term observations after implantation of the artificial endothelial lamella in eyes with endothelial dysfunction.

MATERIALS AND METHODS

The Artificial Endothelial Layer

EndoArt is a 50-μm thin implant composed of hydrophilic Ci26 copolymer material (Contamac Ltd, Saffron Walden, United Kingdom) that is optically clear and provides high biocompatibility and biostability. With a diameter of 6.0 mm and 6.8 mm anterior curvature, it is designed to match the recipient's posterior stroma upon implantation.

Surgical Technique

As described previously,[11] the central corneal surface was marked using a 9.0-mm ring-shaped marker (Geuder AG, Germany) to outline the peripheral extent of descemetorhexis. Two paracentesis incisions, at 10 o'clock and at 2 o'clock, were followed by a 2.4-mm clear corneal incision at 12 o'clock. A reverse Sinskey hook (Storz Ophthalmic Instruments, Germany) was then used to peel the recipient's Descemet membrane (DM) and endothelium, creating a 9.0-mm descemetorhexis.

The Accuject intraocular lens injector (Medicel AG, Switzerland) was used to load and inject the artificial endothelial layer. Once placed within the anterior chamber, the implant was lifted carefully and positioned onto the bare posterior stroma using a Sauter cannula (Geuder AG). A bubble of air and a bubble of air–gas mixture with 20% sulfur hexafluoride (SF6), and in some cases, 10-0 nylon sutures were used to secure the implant and support adherence.

Postoperative topical regimen included an antibiotic eye drop 3 times daily for 1 week and a low-dose corticosteroid eye drop 3 times daily that was tapered in the first few months.

Clinical Assessment

This retrospective case series included patients who underwent EndoArt implantation for corneal edema because of endothelial dysfunction and had at least 12 months of postoperative follow-up data. Table 1 shows the preoperative characteristics of all patients. Pre- and postoperative assessments included slit-lamp examination and measurements of the corrected distance visual acuity (CDVA) and the central corneal thickness (CCT).

HISTOPATHOLOGICAL ANALYSIS

The surgically removed corneal button was fixed in formalin and processed in the pathology laboratory using standard techniques. Slides were stained with hematoxylin and eosin, and periodic acid Schiff (PAS). Immunohistological analysis was performed using antibodies to cytokeratin AE1/3 (Catalog #760–2595; Roche Diagnostics, Basel, Switzerland) and S100 (Catalog #760–2523; Roche Diagnostics).

STATISTICAL ANALYSIS

Data analysis was conducted using R package (V.4.2.2, R Foundation for Statistical Computing, Vienna, Austria). Clinical variables CDVA and CCT were expressed using the mean ± SD. A paired sample *t* test was performed to compare the variables. A *P*-value of less than 0.05 was defined as statistically significant.

RESULTS

A total of 5 eyes from 5 patients were included in this retrospective analysis. Mean follow-up period was 38.4 ± 20 months (range: 19–72 months). Mean CDVA improved from 1.5 ± 0.7 logMAR preoperatively to 1.1 ± 0.5 logMAR at the last follow-up examination ($P = 0.19$). There was a statistically significant improvement of the mean CCT at the last follow-up (558.4 ± 72.7 μm) compared with preoperative (741.2 ± 88.3 μm) visit ($P < 0.001$) (Table 2). Mean number of total rebubbling procedures was 2.8 ± 1.3.

Case 1

A 58-year-old woman underwent EndoArt implantation for pseudophakic bullous keratopathy (PBK) (CCT = 730 μm) in her right eye because of graft failure after DMEK performed 5 years prior. Given the history of endophthalmitis and the resultant atrophy of the optic nerve and the central retina, the CDVA was 2.3 logMAR, and the patient was informed about uncertain visual prognosis.

EndoArt was implanted with no corneal sutures, and a total of 2 rebubblings, including 1 graft repositioning, were performed. At the last follow-up visit at 6 years postoperatively, both CDVA and CCT had improved to 1.8 logMAR and 496 μm, respectively (Fig. 1).

Case 2

An 82-year-old man presented to our clinic with PBK on his right eye after undergoing DMEK and a rebubbling procedure 2 years ago for treatment of Fuchs endothelial corneal dystrophy (FECD). At presentation, CDVA was 1.1 logMAR and CCT 761 μm. The slit-lamp examination revealed epithelial bullae, subepithelial fibrosis, and stromal edema.

In this patient, DMEK removal was not performed before EndoArt implantation as it was not regarded as necessary by the manufacturer at the time. Postoperatively, he underwent 1 rebubbling procedure, after which the artificial graft remained attached. Although the CCT had improved to 553 μm at 3 years postoperatively, the CDVA worsened to 1.4 logMAR and the subepithelial fibrosis persisted causing visual problems, which led to the patient

TABLE 1. Preoperative Patient Characteristics

Case	Age	Sex	Surgical Indication	Prior Surgical History	Ocular Comorbidities	Preoperative CDVA (logMAR)	Final CDVA* (logMAR)
1	58	F	PBK	•DMEK (2015) •ppV (2013) •CE (2013)	•Optic atrophy •Central retinal atrophy •H/o endophthalmitis (2013)	2.3	1.8
2	82	M	PBK	•DMEK (2018) •CE (2011)	•FECD	1.1	1.4
3	83	M	PBK	•ppV (2020) + secondary iris-fixated IOL implantation •Complicated CE with dropped nucleus (2020) •ppV (2005)	•H/o RRD (2005)	1.7	1.0
4	72	F	FECD	•CE (2009)	•Dry AMD with geographic atrophy	0.6	0.6
5	77	F	FECD	•CE (2022)	•PEX syndrome	1.9	0.7

*At the final follow-up visit; for Case 2 = at the last visit before undergoing PKP.
CF, count fingers; h/o, history of; logMAR, logarithm of the Minimum Angle of Resolution; PEX, pseudoexfoliation syndrome; RRD, rhegmatogenous retinal detachment.

wishing to undergo PKP. The corneal button obtained during keratoplasty was sent for histological analysis (Fig. 2). PAS staining of the cornea revealed a thin, sparsely cellular connective tissue membrane composed of fibroblasts and extracellular matrix covering the EndoArt, which is visible as a translucent and refractile foreign material behind the DM. Additional immunohistological examinations showed neither epithelial (cytokeratin AE1/3) nor endothelial (S100 protein) cells in the connective tissue membrane.

Case 3

An 83-year-old man presented to our clinic with PBK on his left eye resulting from a series of ocular surgeries performed elsewhere, including 1) a retinal surgery for retinal detachment 16 years prior and 2) a complicated cataract surgery, which resulted in lens dislocation into the vitreous that required 3) another pars-plana vitrectomy. His CDVA and CCT on the left eye were 1.7 logMAR and 859 μm, respectively.

EndoArt was implanted and secured with an air–gas bubble and a single corneal suture at 12 o'clock. In the first 6 postoperative weeks, a total of 3 rebubblings were performed, after which the artificial lamella remained adherent to the posterior stroma. At the last follow-up visit at 3 years postoperatively, the CDVA and CCT had improved to 1.0 logMAR and 651 μm, respectively (Fig. 3).

TABLE 2. Preoperative and Postoperative CCT Values

Case	Preoperative	1 yr	1.5 yrs	2 yrs	3 yrs	4 yrs	5 yrs	6 yrs
1	730 μm	510 μm	539 μm	547 μm	433 μm	447 μm	497 μm	496 μm
2	761 μm	510 μm	527 μm	611 μm	553 μm			
3	859 μm	744 μm	676 μm	661 μm	651 μm			
4	682 μm	568 μm	482 μm					
5	774 μm	567 μm	545 μm	597 μm	552 μm			

Case 4

A 72-year-old pseudophakic woman was referred to our Cornea Services for treatment of FECD. On clinical examination, the patient demonstrated bilateral corneal guttae and dry age-related macular degeneration with geographic atrophy in the central retina. On her right eye, CDVA and CCT were 0.6 logMAR and 682 μm, respectively, and on the left eye, CDVA and CCT were 0.5 logMAR and 659 μm, respectively. We recommended DMEK on her right eye first and informed the patient about the reduced visual prognosis because of retinal atrophy from age-related macular degeneration. However, the patient refused to receive a human donor tissue for treatment of her FECD, citing religious reasons. We then explained to the patient that either Descemet Stripping Only (DSO) or EndoArt implantation are possible as alternatives, but DSO would not be recommended as the corneal guttae were already evident even in the peripheral cornea. The patient agreed to undergo EndoArt surgery on her right eye.

A total of 4 rebubblings were performed in the first postoperative month, after which the artificial lamella remained attached. At 12 months postoperatively, the right eye showed subepithelial fibrosis in the central cornea, which was treated via superficial keratectomy. At 18 months postoperatively, CDVA and CCT were 0.6 logMAR and 482 μm, respectively, and the central cornea remained clear (see Supplemental Figure, Supplemental Digital Content 1, http://links.lww.com/ICO/B884).

Case 5

A 77-year-old woman presented to our clinic with PBK that developed after undergoing cataract surgery in her left eye with FECD. The CDVA was 1.9 logMAR and CCT 774 μm. We recommended DMEK as the eye did not have

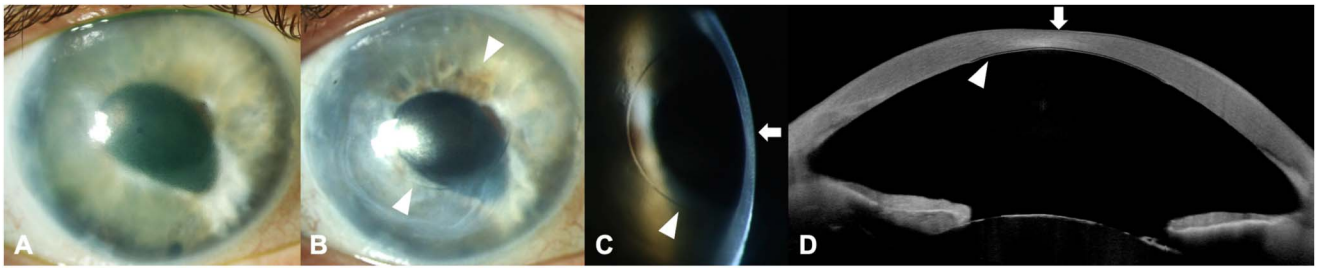

FIGURE 1. Case 1. A, Preoperative slit-lamp image with PBK. B–D, EndoArt in place (white arrowheads) at 6 years postoperatively with the reduction in CCT (white arrows).

any complex ocular comorbidity other than a pseudoexfoliation syndrome. However, the patient did not wish to receive any human donor tissue for personal and ethical reasons and asked for an alternative. After detailed consultation, the patient agreed to undergo EndoArt implantation.

After a total of 4 rebubblings in the first 3 postoperative months, the artificial lamella remained adherent to the host cornea. At 3 years postoperatively, CDVA and CCT had improved to 0.7 logMAR and 552 μm, respectively, and the central cornea remained clear (see Supplemental Figure, Supplemental Digital Content 1, http://links.lww.com/ICO/B885).

DISCUSSION

This study analyzed the long-term efficacy and safety of the artificial endothelial layer for treatment of endothelial dysfunction. Our data demonstrate that the synthetic implant can reduce the corneal edema effectively with no serious adverse events but higher rebubbling rates than EK. One patient (Case 2) underwent PKP 31 months after EndoArt implantation because of visually significant subepithelial fibrosis. Histological analysis of the corneal button obtained during keratoplasty showed a retroprosthetic fibrocellular response to the artificial lamella that may potentially play a role in aiding graft adherence to the posterior stroma.

A variety of treatment approaches have been introduced in recent years to treat corneal endothelial diseases in lieu of EK. In 2018, Kinoshita et al[22] demonstrated that intracameral injection of cultured human corneal endothelial cells combined with a ROCK (Rho-associated protein kinase) inhibitor into eyes with bullous keratopathy can achieve notable visual improvement and reduction of corneal edema at 6 months postoperatively. Despite its innovative concept and promising long-term results,[23] however, culturing of corneal endothelial cells requires specialized cell culture facilities, is subject to stringent regulatory requirements, and carries high cost related to cell processing and transportation, which may hinder its widespread clinical adoption. Surgical approaches that obviate the need for a human tissue such as DSO involves selective removal of the central DM and has been shown to allow endothelial repopulation of the central cornea via migration and proliferation of healthy endothelial cells in the peripheral cornea.[24] Although minimal-invasive and tissue-sparing, the procedure is highly restrictive to early-to-moderate FECD eyes with normal peripheral endothelium without any corneal guttae in the periphery and variable in its efficacy with some eyes demonstrating delayed or incomplete recovery, ultimately requiring an EK. Alternatively, genetic therapy approaches, such as those that aim at repeat cytosine-thymine-guanine (CTG) expansions within TCF4 in patients with FECD, may help prevent disease development even at an early stage.[25] Although it holds much promise, however, its efficacy has yet to be shown in clinical trials.

The synthetic endothelial lamella has gained much global attention since receiving the Conformité Européene mark in Europe and Breakthrough Therapy designation by the United States Food and Drug Administration. Upon our first report of its compassionate use in 2 patients with chronic corneal edema in 2021,[11] numerous studies have reported their outcomes with the artificial implant.[12–21] In countries with limited access to human donor tissues because of logistic, religious, or ethical restrictions, it may be implanted as a primary procedure instead of an EK. In

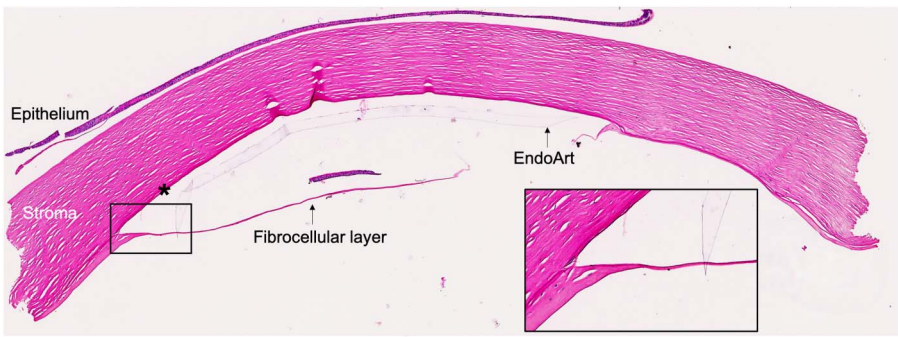

FIGURE 2. Case 2. PAS staining of the corneal button shows EndoArt as a translucent, refractile, partly folded foreign material posterior to the strongly PAS-positive DM (asterisk) (5× magnification). This is covered by a very delicate, cell-poor, connective tissue membrane toward the anterior chamber consisting of fibroblasts and extracellular matrix. The black rectangle indicates the area of the enlarged inset image.

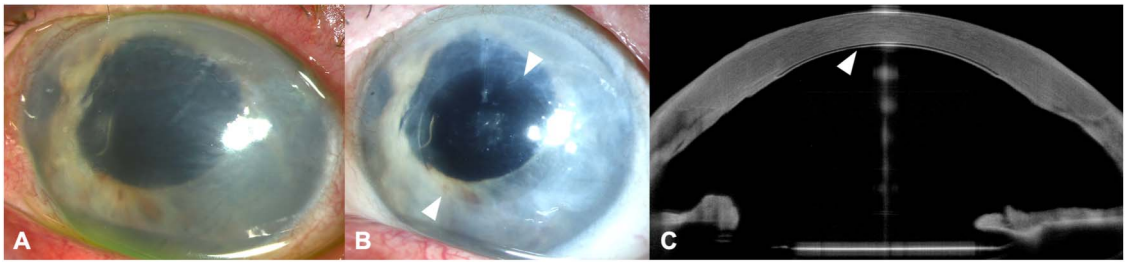

FIGURE 3. Case 3. A, Preoperative slit-lamp image of PBK on the left eye. B–C, At up to 3 years postoperatively, EndoArt (white arrowheads) effectively reduced the corneal thickness and led to clearing of the central cornea.

other countries, it provides an alternative to complex eyes such as those considered high risk for biological tissues, that is, eyes with a history of multiple failed EKs or PKs,[12,14,15] eyes that are aniridic, aphakic, or vitrectomized,[19] or those with glaucoma drainage devices.[20,21] Despite encouraging initial results, there is a paucity of data on its long-term efficacy and safety.

In this study, we observed a statistically significant reduction of CCT at up to 6 years postoperatively in all patients. CDVA had also improved in all patients except in Case 2, where the preexisting central subepithelial fibrosis continued to develop and limit his vision, ultimately leading to PKP for visual restoration. In our institute, however, EndoArt is usually reserved for complex cases with low visual potential, where the primary goal of treatment lies in reducing the corneal edema, thickness, and ocular discomfort rather than gaining vision. Our results are similar to those observed by 2 other currently available long-term studies, where a significant reduction in CCT and visual improvement were noted at up to 4.5 years postoperatively.[16,18]

A recent study reported a case of a delayed-onset endophthalmitis that occurred 7 months after implantation of EndoArt.[26] This long-term analysis, however, did not observe any serious adverse events related to the artificial lamella. In Case 4, subepithelial fibrosis developed in central cornea at 12 months postoperatively, which was treated via superficial keratectomy. Subepithelial fibrosis is not an uncommon finding in eyes with endothelial dysfunction.[27–30] Chronic corneal edema may lead to repeated epithelial injury and delayed regeneration of the epithelial basement membrane, which allows sustained migration of profibrotic cytokines such as transforming growth factor-beta and platelet-derived growth factor into the stroma. Such prolonged presence of the cytokines promotes differentiation of the stromal cells into myofibroblasts, which secrete disorganized extracellular matrix components, causing fibrosis. As subepithelial fibrosis is known to persist even after successful EK with resolution of corneal edema,[31,32] the subepithelial fibrosis observed in Cases 2 and 4 is likely unrelated to EndoArt and rather associated with chronic corneal edema.

We observed a mean rebubbling rate of approximately 3 per eye, which is comparable with the mean 1.8–3.3 rebubbling rates reported in the current literature after EndoArt implantation.[15,16,18,33] Among 23 EndoArt cases from a total of 6 studies, Romano et al[14] observed that at least 1 10-0 nylon corneal suture was performed in 91.3% of cases to secure the artificial graft, but 36.4% still required more than 1 rebubbling, suggesting that a transfixing suture may not always prevent a rebubbling procedure.

To date, it is unclear via which mechanism EndoArt remains attached to on the posterior stroma. Using anterior-segment optical coherence tomography, Fontana et al[16] observed a hyperreflective circular band that extends from the margin of the EndoArt to the adjacent posterior stroma in all patients by 3 months postoperatively, which resembles a fibrocellular scar formation often seen after Descemet stripping endothelial keratoplasty whereby the graft becomes integrated to the host cornea. The corneal button obtained during keratoplasty from Case 2 offered a unique opportunity to perform a detailed histological analysis, which commensurate with the observation by Fontana et al. PAS-staining of the excised tissue demonstrated a fibrocellular tissue membrane posterior to EndoArt, which seemed to entrap or cover the synthetic graft at its edges. In the literature, it is reported that retrocorneal membrane (RCM) formation can occur after EK or PKP and is considered to involve an abnormal wound-healing process at the level of posterior stroma.[34–37] Possible mechanism of RCM development includes trans-differentiation of stromal keratocytes into fibroblast-like cells under the influence of transforming growth factor-beta and other cytokines, which leads to their proliferation and secretion of collagen types I and III, fibronectin, and other extracellular matrix components, forming a fibrous layer.[38–40] Indeed, the fibrocellular membrane posterior to the EndoArt lamella highly resembles the histological characteristics of the RCM, and we hypothesize that it may potentially play a role in the adherence of the artificial graft. However, its potential impact on the patients' visual outcome remains unclear and warrants further investigation.

Furthermore, certain recipient factors may still hinder early graft adherence. Donner et al[41] reported that pronounced irregularities in the posterior corneal surface were associated with high detachment rate, suggesting that an EK using a biological tissue may provide better adherence in eyes with highly irregular posterior elevation. Furthermore, Lapid-Gortzak et al[18] observed an inverse relationship between the preoperative corneal thickness and graft adherence rate, stating that very advanced edema may prevent graft attachment. Future studies with larger sample size are necessary to investigate what recipient factors affect the graft adherence to aid surgeons in selecting the optimal patient candidate for EndoArt.

In this study, the artificial endothelial lamella was implanted as a primary procedure in 2 eyes with FECD (Cases 4 and 5) with no surgical history other than cataract surgery. Generally, we perform DMEK in these eyes as it would likely deliver superior surgical outcomes. However, both patients rejected the use of a human donor tissue, questioning the religious and ethical aspects of a donor graft. To our knowledge, this is the first report of EndoArt used as a primary graft in eyes with endothelial dysfunction, and our results show that effective reduction of CCT can also be achieved in these patients. Nonetheless, whether EndoArt shows greater functional benefit in eyes with no ocular comorbidities or demonstrates an overall comparable efficacy as DMEK remain to be seen in future studies.

This study is not without limitations. In addition to the small sample size, this analysis investigated the CCT and CDVA as primary study parameters in alignment with previous studies on EndoArt. However, several imaging biomarkers are being increasingly recognized as objective key indicators for assessment of the severity of subclinical or clinical corneal edema.[42–44] Future studies that include such parameters may improve the diagnostic precision and allow more nuanced interpretation of corneal deturgescence and clinical response over time.

Nevertheless, this retrospective case series offers the longest follow-up analysis of the artificial endothelial layer reported to date and confirms its efficacy in reducing corneal edema in patients with endothelial dysfunction. Our histological analysis provides insight into potential mechanism of its long-term adherence to host cornea; however, further research is warranted to identify factors associated with graft detachment to optimize the patient selection and surgical outcomes and reduce the rebubbling rates.

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