Artificial Endothelial Layer Implantation After Multiple Failed Keratoplasties

Jasmien Rens, MD,† Iva Krolo, MD,*‡§ Carina Koppen, MD, PhD,*† and Sorcha Ni Dhubhghaill, MBBCh, PhD, FEBOS-CR*†‡§*

Purpose: Presenting the first case of noncellular corneal endothelial substitute after multiple failed penetrating keratoplasty and lamellar endothelial keratoplasty.

Methods: Our case presented with pseudophakic bullous keratopathy after a history of 2 rejected PKs and 1 rejected Descemet stripping automated endothelial keratoplasty. We implanted an artificial endothelial layer.

Results: The implant remained fully attached for a follow-up period of 12 months, and central corneal thickness decreased significantly. The patient reported improvement in her subjective vision, although ocular comorbidities limited the visual potential.

Conclusions: This new device could serve as an alternative to lamellar endothelial corneal transplantation in cases where tissue rejection has occurred and is highly likely to recur. The technique is simple, and the deswelling effect on the cornea persisted, although the visual results require further validation in patients with a higher visual potential.

Key Words: corneal transplantation, penetrating keratoplasty, PK, corneal rejection, keratoprosthesis, artificial cornea, corneal edema

(*Cornea* 2024;00:1–5)

Corneal edema occurs because of failure of the pump function of the corneal endothelium.[1] Most cases are caused either by corneal endothelial dystrophies such as Fuchs endothelial corneal dystrophy, or by pseudophakic bullous keratopathy.[2] Three decades ago, these cases were routinely treated by penetrating keratoplasty (PK),[3] but as endothelial keratoplasty techniques such as Descemet stripping automated endothelial keratoplasty (DSAEK) and Descemet membrane endothelial keratoplasty (DMEK) have improved, they have become the gold standard.[4,5] Corneal transplantation is among the most successful forms of transplantation because of the lack of vascularization and lymphatics in the cornea as well as the immune privilege of the anterior chamber. Nevertheless, rejections do occur, and each event increases the risk of rejection in a subsequent graft.[5]

Transplant rejection, if it cannot be reversed, is typically most damaging to the endothelium. This is due to its relatively high density of cells and its exposed position in the anterior chamber.[6] The stroma may remain relatively unaffected, save for the edema, and strategies to renew rejected PK by replacing the rejected endothelium with either DSAEK or DMEK have proven effective.[7]

In complex cases where a high number of rejections have already occurred, the safety and expected graft survival need to be considered. Moreover, in many countries, there is a shortage of donor tissue, making it ethically difficult to use donor tissue in case of high risk of postoperative complications. There is therefore an unmet medical need for an alternative treatment. In this report, we describe 1 such patient and the use of a noncellular artificial corneal endothelium (Fig. 1) after 3 previous corneal transplant rejections with 1-year follow-up.

CASE DESCRIPTION

An 81-year-old lady with a history of multiple previous corneal transplantation rejections for long-standing pseudophakic bullous keratopathy presented requesting an option for improving her vision. She had a history of ankylosing spondylitis that had resulted in multiple episodes of anterior uveitis bilaterally. She underwent cataract surgery in her 50s, which had been complicated by iris synechiae and postoperative inflammation. In her 60s, her left cornea decompensated and the pseudophakic bullous keratopathy was treated with a PK which was complicated postoperatively by an aggressive uveitis and pressure response. A second PK was performed 18 months later which improved her vision for 6 years until it failed, and her vision dropped to counting fingers. At that time, a third PK was not considered wise, thus it was decided to remain conservative. Seven years after the second rejection, DSAEK was performed with the rationale that it was less invasive and that the use of less tissue would result in a lower risk of rejection. Vision improved initially, but 3 years later, the graft irreversibly rejected and vision returned to counting fingers.

Received for publication August 9, 2023; revision received October 20, 2023; accepted November 23, 2023.

From the *Department of Ophthalmology, Antwerp University Hospital, Edegem, Belgium; †Department of Ophthalmology, Visual Optics and Visual Rehabilitation, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerpen, Belgium; ‡Department of Ophthalmology, University Hospital Brussels, Jette, Belgium; and §Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, Jette, Belgium.

The authors have no funding or conflicts of interest to disclose.

Correspondence: Jasmien Rens, MD, Department of Ophthalmology, Antwerp University Hospital, 2650 Edegem, Belgium (e-mail: jasmienrens@icloud.com).

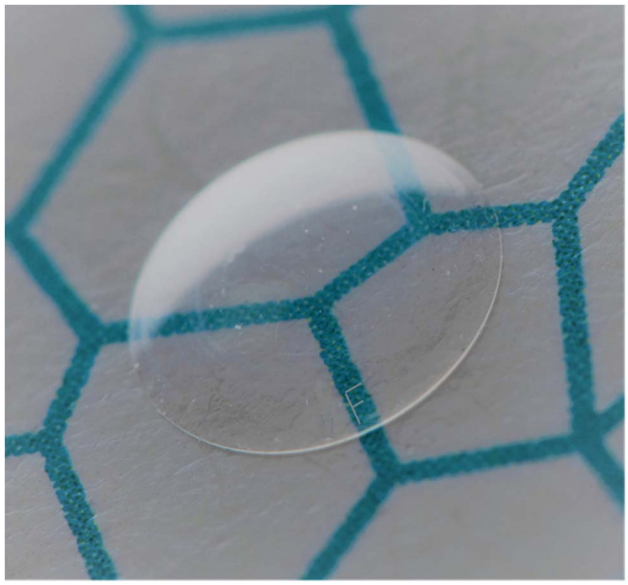

FIGURE 1. Artificial endothelial device showing an F orientation marking (Image courtesy of EyeYon Medical). (The full color version of this figure is available at www.corneajrnl.com.)

On presentation, her vision was still finger counting. The slit-lamp examination showed a hazy cornea due to edema with neovascularization nasally (Fig. 2A). Her systemic ankylosing spondylitis was quiescent under a protocol of etanercept and systemic cyclosporine. Although the DSAEK graft was well attached (Fig. 2B), the central corneal thickness (CCT) measured by anterior segment optical coherence tomography (Tomey Casia OCT, Nagoya, Japan) was 1005 μm (Fig. 2C). After a lengthy discussion regarding the risks and potential benefits, the patient consented to surgery with a new medical device, an artificial endothelium (EndoArt, EyeYon Medical, Ness Ziona, Israel) with the aim of improving the corneal edema and her visual acuity. A corneal transplant was reserved postoperatively in case the device needed to be replaced, although this was not required.

Surgery

The procedure was performed under general anesthesia. Corneal epithelium was removed and paracenteses were made at 10- and 2-o'clock positions. A bubble of air was injected and the previous DSAEK grafts were removed using a reverse Sinskey hook (Bausch & Lomb, Concord,

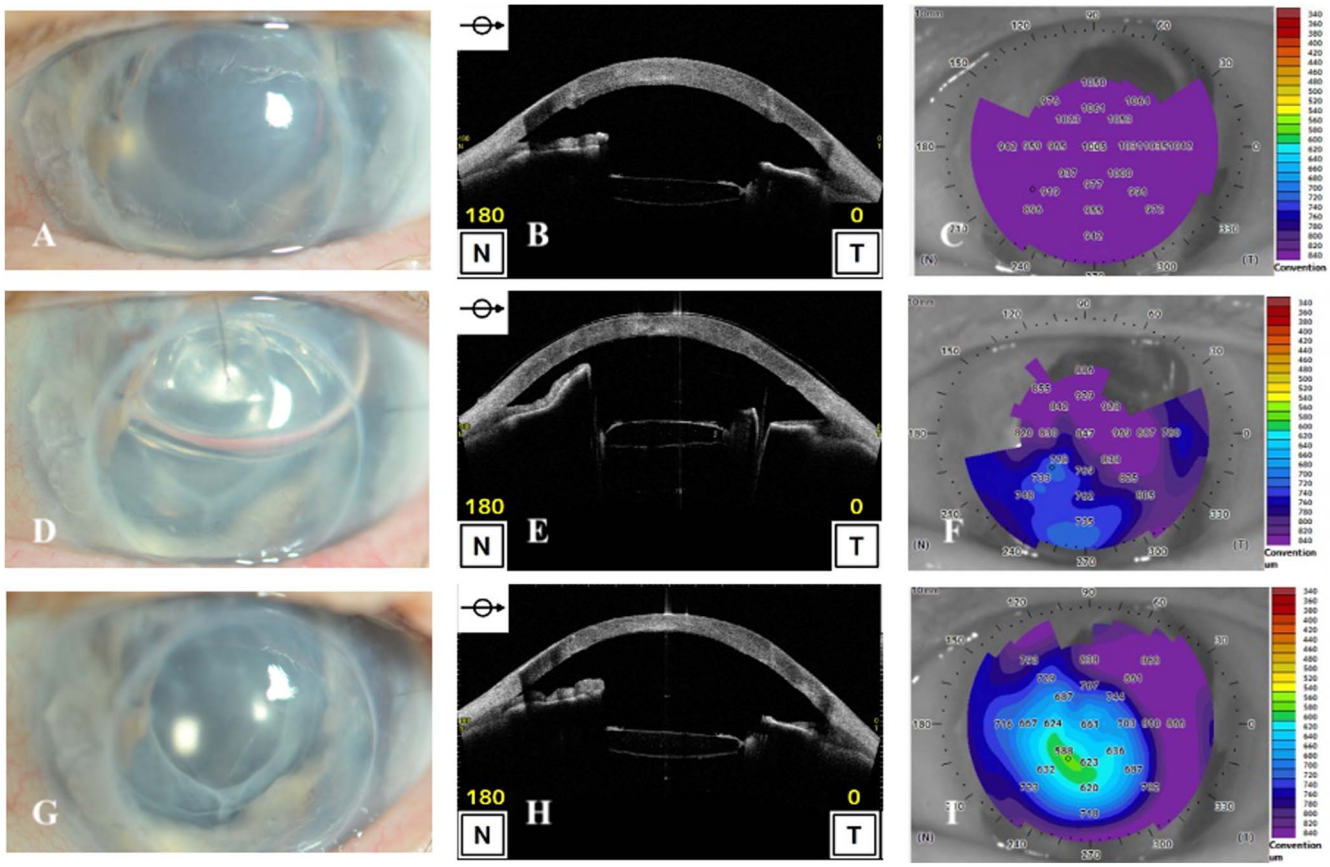

FIGURE 2. Anterior segment photographs of the eye preoperatively (A), after 1 week (D), and after 1 year (G). Anterior segment OCT cross-section images of the eye preoperatively (B), after 1 week showing the synechia (E), and after 1 year (H), showing the iris details that are appearing to be more visible than before surgery. OCT-derived pachymetry of the eye preoperatively (C), after 1 week (F), and after 1 year (I). (The full color version of this figure is available at www.corneajrnl.com.)

ON, Canada) and a pair of descemetorhexis forceps (FR-2299-Descemetorhexis Forceps 25g, Eye Technology, Rayleigh, UK) (Fig. 3A). A 3-step 2.4-mm corneal limbal incision was made at 3-o'clock position to remove the mobilized tissue. An anterior chamber maintainer with an infusion of balanced salt solution was installed and the air removed. The artificial endothelium was introduced into the anterior chamber through the main incision using a lens spatula (Fig. 3B). The orientation mark (F) was confirmed, and air was injected under the implant to position it behind the posterior stroma (Fig. 3C). The implant was sutured at 12-o'clock position using a single nylon 10-0 suture introduced from the peripheral cornea to the center to avoid shifting the device position (Fig. 3D). The anterior chamber was filled to 90% with a mixture of filtered air and 10% perfluoropropane (C3F8) gas. Sectorial iris atrophy was present preoperatively, eliminating the necessity for an iridotomy to prevent ocular pressure elevation. Intraoperative anterior segment optical coherence tomography (Tomey Casia OCT, Nagoya, Japan) confirmed the position of the artificial layer at the end of the procedure (Fig. 4). The combination of gas tamponade and suturing of the device secures attachment in the early postoperative phase. The needle is driven through the implant to attach it to the cornea. The damage to the device is limited, and because it is artificial, this enables us to manipulate it without risking failure, in contrast to conventional lamellar transplants. The attachment is maintained long term with a combination of surface tension forces, healing, and implant design, which features a dome shape to fit the posterior corneal curvature, emphasizing the importance of correct orientation.[8] The orientation of the endothelial artificial layer is checked using an "F" mark that is imprinted on the implant.

Postoperative Course

One day postoperatively, the CCT had decreased to 788 μm, which could be accounted for by the removal of the corneal epithelium and old DSAEK graft. The postoperative topical therapy consisted of topical dexamethasone and tobramycin (Tobradex, Novartis, Basel, Switzerland) drops 4 times daily the first week and was then tapered with 1 drop per week. A supine position was encouraged for the first week. A preexisting anterior iris synechia increased in size postoperatively but did not cause any adverse effects. After 1 month, the postoperative bandage contact lens was removed and an ophthalmic hypersaline solution (ODM5, Horus Pharma, Brussels, Belgium) was administered 4 times daily as a long-term treatment to create an additional deswelling effect. Although it does not accelerate the visual recovery after DMEK and is not the standard regimen that is recommended, we added it to increase corneal clarity.[9] Eight weeks after surgery, the fixation suture was removed and there were no episodes of device detachment. One year after the procedure, CCT was 661 μm, with a thinnest point of 583 μm. Best-corrected visual acuity was 0.13 (decimal Snellen). If we consider the effect of removed DSAEK stroma on the pachymetry, we can calculate the percentage of deturgescence to be 19%, which is comparable to the deswelling effect of DMEK.[10] The cornea was clearer, but her visual acuity was still limited by glaucomatous optic nerve damage.

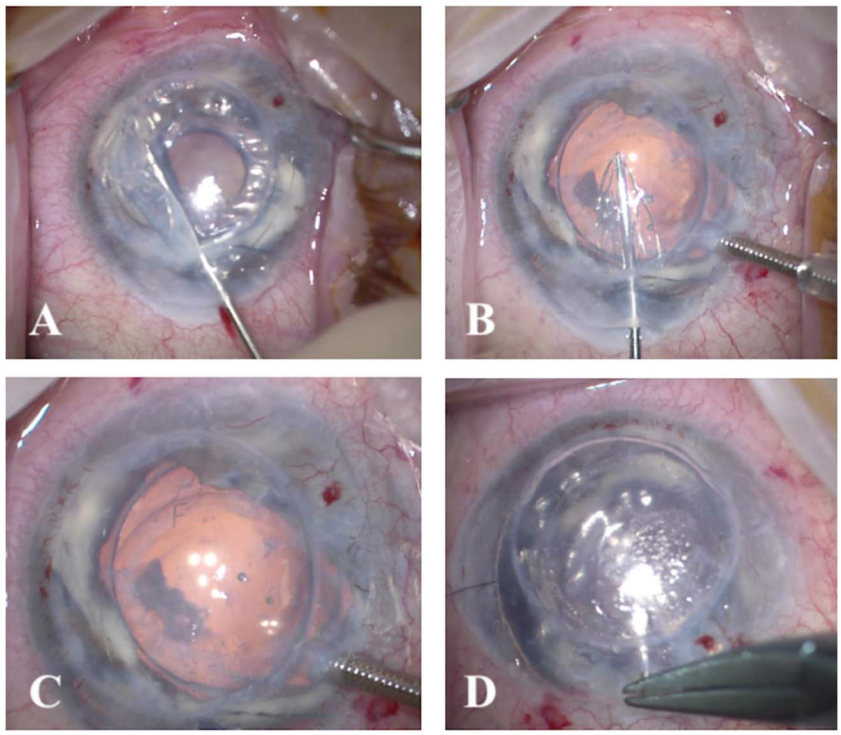

FIGURE 3. Intraoperative course: Removal of previous DSAEK (A), introduction of the artificial layer (B), confirming the F orientation mark (C), and suturing of the device from peripheral to central (D). (The full color version of this figure is available at www.corneajrnl.com.)

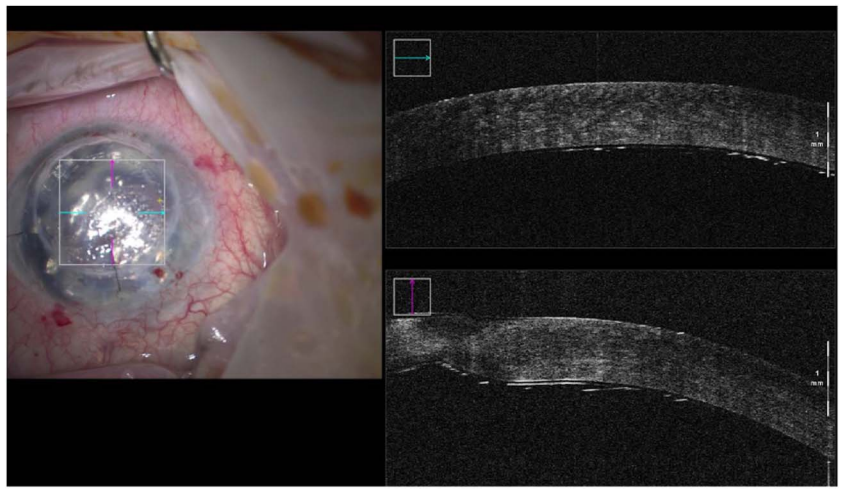

FIGURE 4. Intraoperative anterior segment optical coherence tomography confirming the implant position. (The full color version of this figure is available at www.corneajrnl.com.)

DISCUSSION

When corneal endothelial cells are injured, they have a limited regenerative capacity and when they fail, corneal edema results. The definitive treatment is a posterior lamellar corneal transplantation.[5,11] Although the risk of rejection in lamellar techniques is reduced in comparison with PK, graft rejection remains a concern with all transplants. The 5-year rejection rates with PK, DSAEK, and DMEK are 5% to 17%, 8% to 14%, and 1%, respectively.[6,11,12] Each additional graft is associated with an increased risk of rejection (risk ratio 1.27), meaning the risk ratio of a fourth transplant is 2.07 with a rejection rate of 53% in 3 years.[6,7,13] Aboshina et al[3] estimated that the 5-year survival of a fourth graft, as is the case of this patient, would be 34%. Given this poor graft prognosis and history of postoperative inflammation and pressure increase, this patient was considered too high risk for biological tissue.

When biological tissue is not a viable option, artificial corneas or keratoprostheses can be considered. Although a number of devices have been proposed, the 2 most established approaches are the Boston Keratoprosthesis and osteo-odonto-keratoprosthesis. Boston Keratoprosthesis is the most widely used consisting of a titanium back plate, a polymethylmethacrylate front plate, and a titanium locking ring.[14] The osteo-odonto-keratoprosthesis is an older multistage surgical approach that uses an optical cylinder embedded either in tooth or in bone vascularized using the patient's oral mucosa.[15] Both prostheses are typically reserved for ocular surface cases that have a high risk of rejection when treated with human tissue, such as Stevens–Johnson syndrome, autoimmune diseases with chronic inflammation, or severe ocular burns.[16] The main limitations of keratoprosthetics are the postoperative complications such as retroprosthetic membranes, glaucoma, device extrusion, and endophthalmitis.[15,16] After discussing with the patient, neither a repeated graft nor a keratoprosthesis was considered a viable option for her, primarily due to the potential complications they carried. In addition, the presence of functioning stroma and epithelium made the lamellar endothelial technique the preferred treatment approach.[16] The EndoArt artificial endothelium had not yet been used after PK, but given the lower degree of manipulation and reported successes, she agreed and gave informed consent.

The artificial endothelial device is Conformité Européene (CE) marked and applied for Food and Drug Administration (FDA) approval. It is a thin hydrophilic polymer film (50 μm) with a diameter of 6 mm that serves as a physical barrier to prevent fluid inflow from the anterior chamber to the stroma, resulting in the establishment of a new steady-state–relieving corneal edema. The device is designed to replace endothelial function in complex cases where human donor tissue has failed or its use is not possible.[17] The hypothesis is that the peripheral posterior surface of the cornea not covered by the implant will allow for sufficient fluid influx and nutrient transport, which will enable a safe corneal physiology, without eliciting events such as corneal melting or perforation. EndoArt was preclinically tested in a porcine animal model, consisting of 34 female swine subjected to unilateral induction of corneal edema by stripping a central disc (7–7.5 mm diameter) of Descemet membrane. The implant provided relief from edema over a follow-up period of 1 year, whereas control eyes continued to suffer from persistent and severe corneal edema.[8,18] By December 2022, the device had been implanted in 101 human eyes with a reduction in CCT in 51 of 77 reported eyes after 4 months, and this result was maintained over a follow-up period of 1 year in 14 eyes.[19] Lapid-Gortzak et al also reported 5 cases of corneal edema, 4 of which improved, although none of these cases were post-PK.[20] As in our case, improvement of visual acuity was limited by preexisting eye pathologies.

The most frequent postoperative complication reported with the device was detachment. This did not occur in our case, and we believe that this was due to a number of reasons. The C3F8 maintained a tamponade for 4 weeks and the fixation suture supported the device until removal at 8 weeks. In the longer term, the patient was diligent in not rubbing her eye and the topical hypertonic saline may have augmented the corneal dehydration effect. We removed the DSAEK graft before implanting the artificial layer. Normally, according to

the manufacturer guidelines, DSAEK grafts should be removed with a possible need for a descemetorhexis enlargement to ensure there is no overlapping with the implant, whereas DMEK grafts can be kept without additional risks involved. In this case, an additional descemetorhexis was not needed. Despite the modest improvement in vision, the subjective report of the patient was very positive. She experienced no adverse events and her anterior chamber and intraocular pressure remained quiescent.

In this case, the use of the artificial endothelial device after PK proved to be safe and effective in improving corneal edema. The surgery was minimally invasive and performed through small incision, and technically simpler than most corneal transplant surgeries. The device elicited only a small amount of postoperative inflammation and remained in place and transparent 1 year postoperatively. The major advantage of this approach is the entirely artificial nature of the implant which will not be rejected, but longer term follow-up is still required to ensure that the device remains effective and safe.

CONCLUSIONS

Implantation of an artificial endothelial layer (EndoArt) is a new promising technique, especially for complex cases where conventional corneal transplantation techniques have a high risk of failure. This case report is the first to describe the use of the device after penetrating keratoplasty where it had a marked effect on the corneal edema as was shown by a 34% decrease in pachymetry. It is a simple surgical technique and adaptations to the technique have reduced the risk of detachment. Long-term follow-up is required, but it is a promising solution for patients at high risk for rejection.

REFERENCES

1. Jeang LJ, Margo CE, Espana EM. Diseases of the corneal endothelium. *Exp Eye Res*. 2021;205:108495.
2. Dunker SL, Armitage WJ, Armitage M, et al. Outcomes of corneal transplantation in Europe: report by the European cornea and cell transplantation registry. *J Cataract Refract Surg*. 2021;47:780–785.
3. Aboshiha J, Jones MNA, Hopkinson CL, et al. Differential survival of penetrating and lamellar transplants in management of failed corneal grafts. *JAMA Ophthalmol*. 2018;136:859–865.
4. Auffarth GU, Son HS, Koch M, et al. Implantation of an artificial endothelial layer for treatment of chronic corneal edema. *Cornea*. 2021; 40:1633–1638.
5. Singh R, Gupta N, Vanathi M, et al. Corneal transplantation in the modern era. *Indian J Med Res*. 2019;150:7–22.
6. Hos D, Matthaei M, Bock F, et al. Immune reactions after modern lamellar (DALK, DSAEK, DMEK) versus conventional penetrating corneal transplantation. *Prog Retin Eye Res*. 2019;73:100768.
7. Hos D, Schlereth S, Schrittenlocher S, et al. [Descemet membrane endothelial keratoplasty (DMEK) for graft failure after penetrating keratoplasty and in vascularized high-risk eyes]. *Ophthalmologe*. 2021; 118:536–543.
8. Bachmann BO, Roessler K, Tourtas T, et al. The influence of hypertonic sodium chloride eye drops on the early postoperative course after Descemet membrane endothelial keratoplasty (DMEK). *Invest Ophthalmol Vis Sci*. 2014;55:883.
9. Neiter E, Sot M, Lhuiller L, et al. Relationship between preoperative corneal thickness and postoperative visual outcomes after posterior lamellar corneal transplant. *Int J Ophthalmic Pathol*. 2019;8:1.
10. Price MO, Mehta JS, Jurkunas UV, et al. Corneal endothelial dysfunction: evolving understanding and treatment options. *Prog Retin Eye Res*. 2021;82:100904.
11. Anshu A, Price MO, Price FW Jr. Risk of corneal transplant rejection significantly reduced with Descemet's membrane endothelial keratoplasty. *Ophthalmology*. 2012;119:536–540.
12. Maguire MG, Stark WJ, Gottsch JD, et al. Risk factors for corneal graft failure and rejection in the collaborative corneal transplantation studies. Collaborative Corneal Transplantation Studies Research Group. *Ophthalmology*. 1994;101:1536–1547.
13. Klufas MA, Colby KA. The Boston keratoprosthesis. *Int Ophthalmol Clin*. 2010;50:161–175.
14. Ortiz-Morales G, Loya-Garcia D, Colorado-Zavala MF, et al. The evolution of the modified osteo-odonto-keratoprosthesis, its reliability, and long-term visual rehabilitation prognosis: an analytical review. *Ocul Surf*. 2022;24:129–144.
15. Holland G, Pandit A, Sánchez-Abella L, et al. Artificial cornea: past, current, and future directions. *Front Med (Lausanne)*. 2021;8:770780.
16. Augustin VA, Köppe MK, Auffarth GU. Artificial DMEK could help tackle endothelial donor tissue shortage. *Ophthalmol Times Europe*. 2021;17: 32–34.
17. EyeYon. Unpublished data.
18. Marcovich A. *Artificial Endothelium: An Alternative to DMEK?*; 2022. ESCRS On Demand.
19. Krader CG. *Innovative Breakthrough in Chronic Corneal Oedema*; 2022. Available from: https://www.escrs.org/eurotimes-articles/innovative-breakthrough-in-chronic-corneal-oedema/. Accessed October 6, 2023.
20. van der Meulen I. *Artificial Corneal Endothelial Implant: The EndoART*. ESCRS On Demand; 2021. Available from: https://escrs.conference2web.com/#!resourcegroups/order=relevant&query=endoart. Accessed March 11, 2023.