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The Rapid Transformation of Transplantation for Corneal Endothelial Diseases: An Evolution From Penetrating to Lamellar to Cellular Transplants

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Abstract: The cornea is the major focusing structure of the human eye and the corneal endothelium maintains the relatively dehydrated state of the cornea required for clarity. The endothelial cells respond to disease or injury by migration and cellular enlargement. Our current understanding is that there is a very limited degree of proliferative or regenerative capacity in the human corneal endothelium. Thus, corneal endothelial diseases may result in corneal edema, significantly impact vision and quality of life. Contemporary surgical transplantation options for treating moderate to advanced endothelial dysfunction include penetrating keratoplasty (PK), Descemet stripping endothelial keratoplasty (DSEK), and Descemet membrane endothelial keratoplasty. Advances in surgical techniques aim to bring faster visual recovery and improve visual outcomes; however, there is still a significant donor cornea shortage worldwide and alternative methods for treatment for corneal endothelial disease are rapidly evolving. Indeed, we are at a pivotal point in corneal transplantation for endothelial disease and novel surgical strategies include using 1 donor for multiple recipients, a minimally attached endothelial graft, and Descemet membrane stripping only. Crucially, forthcoming approaches include the use of Rho-Kinase (ROCK) inhibitors, endothelial cell therapy, tissue engineered grafts, and consideration of stem cell techniques. Ultimately, the choice of technique will be dependent on recipient factors such as age, type of endothelial disease, extent of the disease, and associated ocular disorders. The safety and efficacy of these rapidly developing treatments warrant further investigations. In time, some or all of these alternatives for corneal transplantation will alleviate the reliance on limited corneal donor tissue.

Key Words: cornea, endothelial keratoplasty, endothelium, keratoplasty, ROCK inhibitor

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Corneal endothelial cells play a crucial role in regulating corneal hydration. However, these cells are known to undergo very little or no proliferation in vivo and typically respond to reduced density by migration and cellular enlargement.[1] Therefore, disease or injury to these cells may result in corneal edema and loss of corneal transparency; hence, significant visual loss, including blindness, may occur.

Corneal endothelial diseases affect all ages, have a significant impact on vision and quality of life, and have obvious economic implications subsequent to visual impairment. The most common endothelial disorders leading to transplantation, Fuchs' endothelial corneal dystrophy (FECD) and pseudophakic bullous keratopathy, predominantly affect older age groups.[2] Iridocorneal endothelial syndrome is usually observed in middle age, typically affecting only 1 eye and being a much less common indication for transplantation.[3] In contrast, posterior polymorphous dystrophy and congenital hereditary endothelial dystrophy both affect young children. As mild endothelial disease is usually asymptomatic,[4] the true incidence of corneal endothelial disease remains unknown.

Treatment of corneal endothelial disease is usually only necessary once the cornea begins to decompensate and develops a degree of corneal edema. In early cases of corneal decompensation, vision may be temporarily maintained by simple strategies to reduce the hydration of the cornea. These may include the use of 5% hypertonic saline drops or ointment,[5] using a hairdryer held at arm's length to blow cool air over the cornea to increase evaporation,[6] or reducing the intraocular pressure (IOP) to decrease fluid flow across the endothelial barrier.[6] However, in moderate to advanced endothelial dysfunction, surgical intervention in the form of corneal transplantation is typically required to restore vision.

EVOLUTION OF CORNEAL TRANSPLANTATION

The first successful human corneal transplant was performed by Eduard Zirm (1887–1948) in Louts near Prague in 1905.[7] Subsequent developments in antiseptic principles, anesthesiology, surgical technique, and immunology led to improved surgical methodology, technology and instrumentation, postoperative management, and visual outcomes.[8]

In the ensuing decades, particularly since the 1960s, the number of corneal transplants performed each year has increased globally.[9]

Until relatively recently, penetrating keratoplasty (PK) has been the mainstay surgical procedure for the management of corneal endothelial disease. However, the last 15 years have seen a renaissance in, and wide acceptance of, posterior lamellar techniques which selectively replace the corneal endothelium.

Descemet stripping automated endothelial keratoplasty (DSAEK) involves transplantation of the Descemet membrane (DM)-endothelial complex with a thin layer of posterior corneal stoma, and Descemet stripping automated endothelial keratoplasty (DSAEK), a version of DSEK where donor tissue is cut using an automatic microkeratome, instead of by hand. Descemet's membrane endothelial keratoplasty (DMEK) involves transplantation of the DM-endothelial complex in isolation.

The development of these lamellar techniques has seen the demand for endothelial grafts increase significantly.[2] In New Zealand, where keratoconus is by far the leading indication of corneal transplantation, endothelial keratoplasties comprised 39% of all procedures in 2018, with 31% DSAEK and 8% DMEK (personal communication, L. Moffat, New Zealand National Eye Bank, April 2019). In Australia and the United States, DSAEK and DMEK together account for more than half of all corneal grafts.[10,11] In the United States, where lamellar corneal surgery overtook penetrating surgery in 2011, the most common indication of endothelial corneal transplantation is FECD (49.2%), followed by pseudophakic bullous keratopathy (17.2%), and repeat transplant (8.8%).[12]

PK

PK is a very well-established technique and remains the most commonly performed type of tissue transplantation worldwide.[13] The absence of a tissue interface in the visual axis allows optimum optical clarity of the transplanted tissue, making 20/20 vision possible, usually with the aid of spectacles or contact lenses. In addition, the long-term survival of full thickness corneal grafts has been reported to be as high as >90% at 10 years in low-risk cases.[14]

Despite the successes in terms of visual outcomes and survival, PK has a number of limitations. The "open sky" aspect of the procedure is associated with intraoperative risks such as expulsive hemorrhage and iris prolapse, and postoperative complications such as anterior synechiae and endophthalmitis.[15] Common postoperative complications include raised IOP, loose or broken sutures, and corneal allograft rejection, each of which has been reported to occur in approximately 30% of PK.[15] The need for prolonged topical corticosteroids is associated with complications including raised IOP and cataract.[16] Ultimately, corneal astigmatism is the most common cause of suboptimal vision in the presence of a clear graft,[17] with approximately one third of eyes having ≥5.00 diopters of corneal astigmatism after PK.[18]

DSEK/DSAEK

Lamellar surgery offers a number of advantages over PK. It avoids the "open sky" segment of surgery, therefore limiting the associated complications observed during PK.[19]

In DSEK/DSAEK, the donor button comprises endothelium, DM, and a thin layer of deep stroma. This procedure is less invasive than PK, and requires minimal or no sutures. The preservation of host corneal structure and shape with minimal addition of tissue results in a tectonically stronger eye. Postoperatively, topical corticosteroids are used for a shorter period, thereby minimizing corticosteroid-related complications such as elevated IOP. In 2009, a major review of DSEK/DSAEK in 2,722 eyes published in 34 substantial articles demonstrated the safety and outcomes of these procedures.[20] Importantly, visual rehabilitation occurs more rapidly, typically over a period of weeks rather than months, mainly due to lower surgically induced astigmatism and ametropia. Other advantages include fewer graft rejection episodes and less intensive patient follow-up.[20]

The most common adverse events included graft dislocation in 14% (range 0–82%), primary graft failure in 5% (range 0–29%), endothelial rejection in 10% (range 0–45%), and iatrogenic glaucoma in 3% (range 0–15%). Although graft dislocation was the most common complication after DSEK, if managed appropriately, it is not sight threatening compared with PK dislocation/graft-host junction disruption. It can be treated by injecting air into the anterior chamber, to form a large bubble that apposes the donor graft against the host tissue to promote attachment (also known as a rebubble procedure). Endothelial cell loss at 1 year was significant and ranged from 24% to 61%, with an average of 41% cell loss. Based on these results, the American Academy of Ophthalmology (AAO) concluded that DSEK was superior to PK in terms of earlier visual recovery, refractive stability, refractive outcomes after surgery, wound and suture-related complications, and suprachoroidal hemorrhage risk during and after surgery.[20] They also concluded that DSAEK was comparable with PK in terms of surgical risks, complication rates, graft survival (clarity), visual acuity, and endothelial cell loss.[20]

A subsequent study of 1223 eyes that underwent DSAEK between 2012 and 2014 with 5-year follow-up showed late endothelial graft failure occurred in 1.3% of eyes.[21] Interestingly, endothelial cell density at 6 months postoperatively and intraoperative complications were each significantly associated with late endothelial graft failure.[21]

Despite the substantial initial endothelial cell loss, the 5-year graft survival rates of DSAEK have been reported to be comparable to those of PK (95% in Fuchs' endothelial dystrophy, 76% for bullous keratopathy).[22] Notably, the mean endothelial cell loss at 5 years postoperatively in this large series was 53%.[22] Keane et al[23] reported evidence of the existence of a national surgeon learning curve for DSEK/DSAEK in Australia. The authors concluded that once 56 of such grafts had been performed, subsequent graft survival was not affected by further experience.

DMEK

DMEK involves transplantation of the DM-endothelium complex and is more surgically challenging than DSAEK. Much of the challenge relates to difficulties in unrolling the donor scroll once inserted into the anterior chamber. Although the mean DMEK rebubble rate to manage graft detachment (mean 28.8%, range 2.4%–82%)[24] is typically reported to be much higher than that for DSAEK (mean 14%, range 0–82%),[20] the ranges are similar and the rebubble rate decreases with increased surgeon experience performing DMEK.[24]

DMEK has been demonstrated to offer some advantages over DSAEK. A report by the AAO reviewing the published literature on DMEK confirmed faster visual recovery and better visual outcomes with DMEK compared with DSAEK, with 50% to 55% achieving best-corrected visual acuity (BCVA) of ≥20/25 6 months after DMEK compared with 6% to 31% at 6 months after DSAEK.[24] The endothelial rejection rate after DMEK (1.9%) is also significantly lower than that after DSAEK (10%). Despite the reported lower rate of allograft rejection, the 5-year graft survival rate of DMEK (93% in Fuchs' endothelial dystrophy) is comparable to that reported for DSAEK and PK[25], and this apparent anomaly requires to be further illuminated by longer-term follow-up.

Endothelial cell loss has been reported to be comparable between the 2 endothelial procedures over time.[24,25] The mean endothelial cell loss after DMEK being 33% (range, 25%–47%) at 6 months,[24] and 48% at 5 years.[25] Perhaps surprisingly, a large multicenter study of 2485 DMEK eyes reported that visual acuity outcomes and endothelial cell loss at 6 months did not correlate with surgeon experience with DMEK.[26]

Overall, it may be concluded on the basis of contemporary published data that compared with DSAEK, DMEK provides a faster visual recovery, better visual outcome, and lower risk of rejection, but is associated with a higher rebubbling rate.

FUTURE ALTERNATIVES TO CONVENTIONAL ENDOTHELIAL KERATOPLASTY

Although surgical techniques for corneal transplantation have evolved and the success of this procedure has improved substantially over the half-century, there are still significant limitations. In particular, a global major issue is the paucity of donor tissue (only 1 cornea available for potentially every 70 required).[27] Alternative forms of treatment for corneal endothelial disease are therefore being sought at this pivotal time in the ongoing quest for improved surgical and medical treatments for corneal diseases.

Hemi- and Quarter-DMEK

One way of overcoming the problem of shortage of donor tissue is to use one donor cornea to treat multiple patients. Some success has been reported on inserting half (hemi-DMEK) or quarter (quarter-DMEK)-sized DMEK grafts after creating a circular Descemetorhexis in patients with FECD. 6 months after hemi-DMEK, 70% of eyes achieved BCVA of $\geq$20/40 with a mean reduction in central corneal thickness of 255 μm.[28] 6 months after quarter-DMEK, all eyes achieved BCVA of $\geq$20/40 with a mean reduction in central corneal thickness of 120 μm.[29] Interestingly, rebubbling was required in a high percentage of patients receiving hemi-DMEK (40%) and quarter-DMEK (33%). In both studies, endothelial cells filled in denuded areas, suggesting that the corneal endothelium does have some regenerative capacity in vivo, although it is unclear whether this regeneration originated from the donor cells or the recipient endothelium.

Descemet Membrane Endothelial Transfer

The results of hemi- and quarter-DMEK raise the question of how small the donor transplant can be, yet be able to repopulate a normal-sized descemetorhexis. Notably there have been multiple reports involving >30 patients who achieved corneal clearing as early as 2 weeks postoperatively, despite endothelial graft detachment.[30–34] These reports suggest that complete graft attachment is not essential for reendothelialization to occur, leading researchers to explore the potential of transplanting a “free-floating" Descemet roll with the edge of the graft sutured to the corneal incision to ensure a focal area (bridge) of contact.

When this procedure, termed Descemet membrane endothelial transfer (DMET), was performed in eyes with FECD (n = 7), progressive corneal clearance was observed at 6 months postoperatively, with a mean decrease in central corneal thickness of 100 μm and mean endothelial cell density of 797 cells/mm^2.[35] However, in eyes with bullous keratopathy (n = 5), there was no improvement in any of these parameters and no reendothelialization after DMET.[35] Importantly, eyes with FECD had relatively normal, healthy peripheral corneal endothelium, whereas eyes with bullous keratopathy eyes did not. These results suggest that reendothelialization in DMET may be dependent on a relatively healthy recipient peripheral endothelium, without ruling out the possible contribution from the donor graft endothelial cells toward reendothelialization.

There is further evidence for corneal endothelial cell migration from the recipient periphery. In 2 cases of early DMEK detachment previously noted, corneal clearing and thinning was initially observed at the site of graft detachment, progressively extending to the rest of the cornea, strongly suggesting migration of peripheral endothelial cells as a wound healing response, resulting in redistribution and confluence of endothelial cells in the denuded cornea.[31,32] Also, in cases of the DMEK graft being reversed and the endothelium inserted onto the recipient cornea in the incorrect orientation, corneas have shown clearance from detached areas rather than attached areas, suggesting that the upside-down attachment was a physical obstruction to endothelial migration.[36] PK buttons excised 1 to 30 years after PK showed a mixture of recipient and donor cells, confirming that migration from the recipient can definitely occur over a long period of time.[37] In multiple cases wherein a piece of healthy endothelium and DM was accidentally removed during cataract surgery, the corneas cleared without any graft; therefore, the source of endothelial cell confluency and subsequent corneal clearing can only be endogenous.[34]

Descemetorhexis Stripping Without Endothelial Keratoplasty

The results of DMET and the aforementioned studies suggest that the periphery of the recipient cornea has the ability to repopulate the denuded corneal stroma after intentional or accidental Descemetorhexis, in the absence of a well attached graft (owing to detachment, upside-down grafts, or lack of donor tissue at the time of accidental Descemetorhexis). This naturally raises the question of whether corneal endothelial diseases can be treated by simple Descemet stripping without endothelial keratoplasty (DWEK).

To date the results of DWEK have been controversial. Indeed, an early study by Bleyen et al[38] reported poor results using this technique in FECD (n = 8), with only 1 eye exhibiting a clear cornea and improved vision at 18 months postoperatively. However, the diameter of the descemetorhexis was not reported. Another case study described reendothelialization within 1 month in 2 patients undergoing DWEK[39]: in 1 eye with a large diameter accidental Descemetorhexis, BCVA improved to 6/6 within 1 month, with central corneal endothelial density of 753 cells/mm^2; in the other eye with FECD and a planned 4- to 5-mm mm diameter descemetorhexis, BCVA improved from 6/12 to 6/6–1 after 6 weeks, with central corneal endothelial density of 731 cells/mm^2 by 6 months.[39] In another study, 4-mm diameter DWEK was performed on 13 FECD eyes.[40] In 10 eyes, the cornea cleared within 6 months and endothelial densities ranged from 428 to 864 cells/mm^2. Factors that distinguish this study from the first include the relatively small area of Descemet stripping and the confirmed intactness of the peripheral endothelium.

These studies suggest that reendothelialization of the stripped cornea is dependent on healthy peripheral endothelium and a sufficiently small diameter descemetorhexis. Based on anterior segment optical coherence tomography measurements of healthy adults in Japan, the average area of the posterior surface of adult corneas was 147 mm^2 with an endothelial cell count of

397,000.[41] An 8.5-mm descemetorhexis therefore removes 63.9 mm^2 and 172,000 cells (43% of all endothelial cells).[41] Assuming the area is proportional to the $radius^2$, an 8.5-mm diameter (4.25-mm radius) area is 4.5 times larger than a 4-mm diameter area. By extrapolation, we estimate that a 4-mm descemetorhexis removes approximately 14.2 mm^2 (63.9/4.5) and 38,222 cells (10% of all endothelial cells, 172,000/4.5), leaving 90% of cells to migrate or divide to replenish the 10% lost. In these Fuchs' dystrophy eyes, it may mean that it takes a reserve of 9 cells to replenish 1 lost. A higher number of cells in reserve may be necessary when the disease is more advanced, as in the nonresponders in the previous study (3/13 subjects with 4-mm DWEK).[40]

Indeed, these nonresponders had higher preoperative central corneal thickness than the responders.[40] Alternatively, the number of cells in reserve could be lower in subjects with healthy endothelium, such as those that had accidental descemetorhexis during cataract surgery.

In addition, a collective analysis of outcomes of primary and iatrogenic descemetorhexis revealed that a significantly higher proportion of older patients (>60 years) achieved BCVA of LogMar $\leq$0.3 (20/40 Snellen equivalent), compared with those <60 years.[42] Certain genetic variations in FECD are also associated with worse endothelial recovery and greater disease severity.[42] The applicability of DWEK is therefore limited by the migratory and/or proliferative capacity of the remaining peripheral corneal endothelium, which is dependent on patient age, presence/absence of disease, and type and severity of endothelial disease. DWEK may be worth considering in selecting patients with visual degradation from central guttae in FECD because it does not require donor tissue, cannot induce rejection, does not require long-term topical corticosteroid, and it is always possible to perform an endothelial keratoplasty if DWEK fails.[43]

ROCK Inhibitors

If the limited capacity of the peripheral corneal endothelium to proliferate could be stimulated, DWEK could potentially be performed with a larger diameter and/or in patients with more advanced disease. This has been achieved via the use of a Rho-associated, coiled-coil serine/threonine protein kinase (ROCK) inhibitor in a small study.[43] Rho GTPases, including RhoA, play important roles in the regulation of actin dynamics and actin-associated cellular processes including cell movement, adhesion, stiffness, and morphology.[44] ROCK is a well-studied downstream effector of RhoA, and regulates cellular contraction in smooth muscle tissues mainly through modulating myosin II activity. [44] Much work has been done to investigate the effects of ROCK inhibitors in corneal endothelial regeneration. In this study, 4 mm diameter DWEK (without ROCK inhibitor) was performed in 12 FECD eyes, and successful in 9, with corneal clearing and BCVA improvement from 0.26 to 0.125 (logMAR) at 6 months.[43] The 3 remaining subjects received salvage therapy with ROCK inhibitor eye drops after halting of corneal clearance. ROCK inhibitor Ripasudil was administered in 2 eyes, 6 times a day for 2 weeks, starting from 2 to 3 months. The corneas cleared within 10 and 14 days, respectively. ROCK inhibitor Y-27632 was administered in 1 eye from 5 months without success. One of the 9 initial responders had a small persistent patch of microcystic edema outside the visual axis; after treatment with Ripasudil from 5 months, the cornea cleared within 2 weeks.[43]

Netarsudil and ripasudil, recently approved for the treatment of glaucoma in the USA and Japan respectively, belong to a new class of drugs known as ROCK inhibitors. They lower intraocular pressure by reversing myofibroblastic changes in the trabecular meshwork and Schlemm's canal cells thereby decreasing outflow resistance.[45] In culture, ROCK inhibitor Y-27632 enhanced corneal endothelial cell proliferation, adhesion, and decreased apoptosis.[46–48] In animal models, it enhanced wound healing and corneal endothelial cell proliferation after corneal endothelial injury.[49,50] The effect of ROCK inhibitor on the human corneal endothelium has been tested in a clinical trial of 8 patients with corneal edema. The central endothelial cells were removed by 2-mm diameter transcorneal freezing. The eyes were treated with Y-27632 eye drops for 7 days. In 4 patients with central corneal edema owing to Fuchs' dystrophy, reduction in central corneal thickness from a mean of approximately 740 μm to 640 μm was achieved at 6 months, with no significant improvement in visual acuity.[50] In 4 patients with diffuse corneal edema owing to laser iridotomy or pseudoexfoliation, no reduction in central corneal thickness was achieved at all.[50] Another pilot clinical study enrolled 3 patients with accidental endothelial damage after cataract surgery.[51] The peripheral endothelium was otherwise healthy. These patients received Y-27632 eye drops for 6 months. All recovered corneal clarity.[51] Although this study lacked no treatment controls and delivery vehicle only control (eye drop formula without the active drug), the results are promising. These two studies suggest that ROCK inhibitor Y-27632 may be effective in promoting endothelial wound healing when the peripheral endothelium is spared.

Cell Therapy

Another potential indication for ROCK inhibitors is as an adjunct to cell therapy, which encompass cultivation of cells, such as corneal endothelial cells to replenish the depleted native cell population.[52]. If cell therapy is successful, cultured human corneal endothelial cells from one donor can supply multiple recipients. However, they suffer from poor attachment to the cornea when injected, when being continuously removed from the anterior chamber.[51] A recent clinical trial enrolled 11 patients with bullous keratopathy and no detectable corneal endothelial cells.[53] After removal of abnormal extracellular matrix in the central 8-mm diameter of DM using a silicon needle, cultured human corneal endothelial cells were injected in Y-27632 containing medium.[53] Patients were placed in a prone position for 3 hours for cells to attach. All eyes had a central endothelial cell density of >500 cells/mm^2 at 24 weeks, with a mean endothelial cell density of 1924 cells/mm^2 at 24 weeks and 1534 cells/mm^2 at 2 years. Mean central corneal thickness reduced from 743 μm preoperatively to 549 μm at 6 months, which remained steady with a mean central corneal thickness of 552 μm at 2 years. Improvement in the BCVA of $\geq$2 was achieved in 9 of 11 patients at 24 weeks.[53] From a safety perspective, no inflammation or immunogenic reaction was observed in the eyes; raised IOP was noted in 1 of 11 patients; there were no abnormalities in general health evaluations or blood tests.[53]

In patients with no residual peripheral endothelium, DMET, DWEK, or ROCK inhibitor alone were unlikely to have helped, because these approaches seem to depend on the presence of relatively healthy peripheral endothelium. Hemi-DMEK and quarter-DMEK may help because grafted cells can potentially

migrate off the grafts to repopulate denuded areas, but the resultant endothelial cell density is likely to be low given the small area transplanted. The combination of cell injection, ROCK inhibitor, and prone positioning has shown efficacy in repopulating the corneal endothelium to a high endothelial cell density; in fact, the endothelial cell density at 24 months was the highest of all the endothelial keratoplasty alternatives reported in this perspective.

Tissue Engineered Grafts

Concurrent to development of cell injection as a technique for endothelial replacement, consideration may need to be given as to whether DM really needs to be replaced. Guttae on DM cause irregularity, which hinders corneal endothelial cell migration,[54] and higher-order aberrations, which affect visual acuity.[55] Therefore when treating FECD, DM is perhaps better removed. However, DWEK alone does not facilitate corneal endothelial cell migration, as they migrate faster on smooth DM than bare stroma.[56] Therefore, some form of smooth basement membrane may be required for the optimal treatment of FECD. In bullous keratopathy, there are no guttae, but DM ruptures (50%), isolated detachment (70%) or detachment associated with rupture are frequent.[57] Thus removal of DM abnormalities and replacement with some form of smooth basement membrane may be required for the optimal treatment of many bullous keratopathy eyes.

Tissue engineered endothelial keratoplasty involves transplanting a thin layer (100 μm) of human corneal stroma and DM seeded with human corneal endothelial cells. This technique in a rabbit model of endothelial injury has shown promising results.[58] Other future alternatives may include artificial DMs, or DMs with unsatisfactory endothelial cell counts, thereby increasing utilization of donor tissue.[42]

Stem Cells

Although human corneal endothelial cells have demonstrated potential for cell therapy, reprogramming of stem cells (SCs) from other sources has been researched by multiple groups. These efforts include the reprogramming of embryonic SCs,[59,60] induced pluripotent SCs,[61–63] eyelid derived precursors,[64] umbilical cord blood mesenchymal[65] and endothelial SCs,[66] corneal stromal SCs,[67] bone marrow derived SCs,[68] and adipose derived SCs.[69] Adult SCs for the corneal endothelium have been identified in the extreme periphery of the cornea in an area called the "transition zone," and have the potential to become a new viable source for corneal endothelial cells.[70,71]

CONCLUSIONS

Surgical treatment options for corneal endothelial diseases have evolved from full thickness corneal transplantation to partial thickness techniques, to transplantation of the DM-endothelium complex only. Each step in the evolution brings faster visual recovery and improved visual outcomes. However, there is still a significant donor cornea shortage worldwide, and alternative forms of treatment to corneal endothelial diseases are rapidly developing. Studies show that the corneal endothelium is not as nonregenerative as commonly believed, and some cases of endothelial dystrophies may not require a large, fully attached graft. As a result, future alternatives to endothelial keratoplasty comprise of multiple potential techniques. The choice will be dependent on recipient factors such as age, presence/absence of endothelial disease, type, and extent of the disease. Diseases or injuries that spare the peripheral corneal endothelium may be treated by hemi-/quarter- DMEK, DMET, DWEK, ROCK inhibitors, or ROCK inhibitor in combination with DWEK. Treatment for diseases that do not spare the peripheral endothelium will be restricted to those that involve transplantation of cells or tissue such as cell therapy in conjunction with ROCK inhibitor, or a traditional transplant. It is hoped that future studies will further demonstrate the safety and efficacy of these alternatives, and clarify patient selection criteria for each treatment. At the same time, insights from these studies will enable us to paint a clearer picture of the limit of regeneration that the corneal endothelium is capable of, and to develop and refine treatments for corneal endothelial diseases, reducing the dependency on the limited donor tissues.

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