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Therapeutic future of Fuchs endothelial corneal dystrophy: An ongoing way to explore

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Abstract:

Fuchs endothelial corneal dystrophy (FECD) is one of the most common corneal diseases that causes loss of visual acuity in the world. FECD is a genetically and pathogenetically heterogeneous disease that results in the failure of corneal endothelial cells to maintain fluid balance and functional homeostasis of the cornea. Corneal edema, central guttae formation, and bullae development are common corneal pathologies. Currently, the mainstay of FECD treatment is surgery. However, limited sources of corneal graft and postsurgical complications remain problematic. In recent years, with advances in medical science and technology, there have been a few promising trials of new treatment modalities for FECD. In addition to new surgical methods, novel modalities can be classified into pharmacological-associated treatment, cell therapy-associated treatment, and gene therapy-associated treatment. In this article, our primary focus is on the most recent clinical trials related to FECD, and we present a stepwise approach to enhance FECD management and ultimately improve patient outcomes. We thoroughly searched for FECD clinical trials and reviewed the study designs, methodologies, and outcomes of each trial conducted within the past decade. It is imperative for physicians to stay up-to-date with these cutting-edge treatment approaches.

Keywords:

Cell therapy, Fuchs' endothelial dystrophy, genetic therapy

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Introduction

Fuchs endothelial corneal dystrophy (FECD) is one of the most common corneal diseases that causes loss of vision and severely affects the patient's quality of life.[1] Today, despite numerous treatment options available, a considerable proportion of patients with FECD eventually require a corneal transplant.[1] In recent years, clinical studies on new treatment modalities for FECD have been boosted by advances in surgical technology, molecular biology, and cell therapy. However, to our knowledge, there is a lack of a comprehensive review of FECD clinical trials, especially nonsurgical treatments. Thus, in this review, we aim to summarize the status of FECD treatment, with a particular emphasis on new clinical trials and related research on nonsurgical treatment options.

Pathogenesis

The corneal endothelium consists of a single layer of flat hexagonal cells arranged in a honeycomb pattern.[2-4] The cornea maintains fluid balance through a combination of noncontinuous tight junctions between corneal endothelial cells that partially resist the inward movement of water and transmembrane pumps that actively control ion transport.[2-4] In addition, the corneal endothelium controls the inward flow of nutrients and the outward flow of metabolic waste.[2] Collectively, the corneal endothelium is essential to maintain the transparency, thickness, and refractive index of the cornea.[2-5]

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More than 100 years ago, Dr. Fuchs published the first case series of FECD.[6] However, despite years of research, the pathogenesis of FECD is yet to be fully understood. FECD is a genetically and pathogenetically heterogeneous disease of the corneal endothelium. In general, FECD is caused by the dysfunction and gradual loss of corneal endothelial cells.[2,7,8] Abnormal control of apoptosis, toxic accumulation of RNA-associated products, mitochondrial DNA damage, endoplasmic reticulum stress, and cell senescence secondary to oxidative stress are all involved in the pathogenesis and progression of FECD.[1,8-13] As the disease progresses, the corneal endothelium eventually fails to maintain fluid balance and functional homeostasis of the cornea. Subsequently, corneal edema developed, progressively affecting all layers of the cornea over time.[1]

Clinical Presentation

In general, FECD can be classified into early- and late-onset types.[14,15] Early-onset FECD begins in the first decade of life, and late-onset FECD mostly begins around the age of 40. Mostly, the early-onset type is more severe than the late-onset type, although both types are treated similarly.[14,15] The progression of FECD generally spans 20 to 30 years. Four clinical stages, described by Adamis *et al*., are commonly employed to categorize the clinical manifestations of FECD[7,14-16] [Table 1]. At stage 1, patients are usually asymptomatic, so most of them are found incidentally on routine health examinations. Corneal specular microscopy shows nonconfluent central guttae and some pigments on the posterior cornea.[15-18] At stage 2, mildly decreased visual acuity in the morning due to corneal stromal edema is the most common symptom.[14-16] On examination, a decrease in the cell density of the corneal endothelium and a confluent central gutta that spreads to the peripheral part of the cornea can be observed.[2,7,8] As FECD progresses to stage 3, patients suffer from a reduction in vision acuity that persists throughout the day, and presentations such as halos in the visual field, photophobia, and epiphora are also common.[14-16] Specular microscopy reveals the formation of epithelial bullae resulting from progressive stromal edema. Occasionally, bullae rupture causes eye pain.[1,14] At stage 4, visual acuity continues to worsen. Chronic corneal edema leads to Descemet's membrane folds, corneal scarring, and corneal fibrosis.[1,14-16] Eventually, severely impaired visual acuity may develop, requiring a corneal transplant as definitive treatment [Figure 1].[1,14]

Table 1: Four stages of Fuchs endothelial corneal dystrophy: Clinical presentation and specular microscopy findings

	Symptom	Presentation under specular microscopy
Stage 1	Asymptomatic	Nonconfluent central guttae
		Some pigments on the posterior cornea
Stage 2	Mild decrease in visual acuity	Decreased cell density of the corneal endothelium
		Confluent central guttae
Stage 3	Moderate decrease in vision acuity	Epithelial bullae
		Possible rupture of bullae
	Halos in visual field	
	Photophobia	
	Epiphora	
	Eye pain	
Stage 4	Severe decrease in vision acuity	Corneal stromal edema
		Endothelial folds
		Corneal scarring and fibrosis
	Blindness	

Adapted from: Adamis AP, Filatov V, Tripathi BJ, Tripathi RC. Fuchs' endothelial dystrophy of the cornea. Surv Ophthalmol 1993;38:149-8

In addition to the clinical stages proposed by Adamis *et al*., other grading systems categorizing the severity of FECD are also available. The modified Krachmer grading system has been used to assess the severity by evaluating the number and size of the corneal guttae and the presence of edema on a slit-lamp examination.[19] In addition, the anterior segment optical coherence tomography (AS-OCT) severity rating system for FECD is a novel grading system proposed by Yasukura *et al*.[19] It rates the severity of the disease by utilizing AS-OCT to observe the presence of guttae and stromal edema.[19] Since AS-OCT provides clinicians with more objective assessments, the AS-OCT severity rating system offers a higher grading consistency among clinicians, compared to the modified Krachmer grading system.[19]

Current Treatment

After visual symptoms begin, FECD patients usually receive hypertonic saline as first-line therapy.[1] However, hypertonic saline only reduces symptoms but does not halt the progression of FECD. Currently, the mainstay and only definitive treatment for FECD is surgery. It is indicated in patients with severe symptoms after conservative, nonsurgical treatments fail to provide satisfactory relief.[1] To date, four surgical procedures are available [Table 2], including penetrating keratoplasty (PKP), Descemet stripping endothelial keratoplasty (DSEK), Descemet membrane endothelial keratoplasty (DMEK), and Descemet's stripping only (DSO).[1]

Before the early 2000s, PKP was the only surgical option for FECD.[1,7,20] This surgery replaces all layers of the cornea with a full-thickness corneal graft. In general, the rate of success is favorable despite the slow recovery of vision.[1,20] PKP is now reserved for late-stage FECD with corneal scarring.[1] In the early 2000s, DSEK was

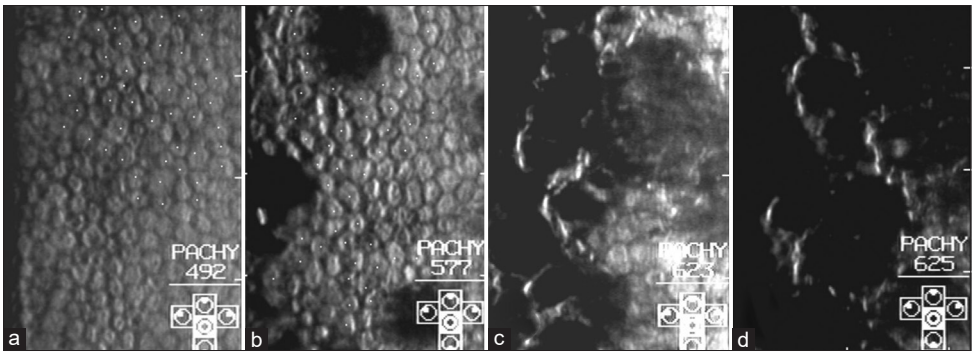

Figure 1: Specular microscopy in different stages of Fuchs endothelial corneal dystrophy (FECD) subjects. (a) Specular microscopy in an early-stage FECD subject. The endothelial cells undergo morphological changes through hexagonal shape and size alterations. (b) Specular microscopy in a stage 1 FECD subject with non-confluent central guttae formation, a dark structure with an occasional central white reflex. (c) Specular microscopy in a stage 2 FECD subject with the formation of confluent central guttae was noticed. (d) Specular microscopy in a late-stage FECD subject with a dark interior surrounded by a bright boundary. No recognizable cells or cell boundaries were seen

Table 2: Current surgical procedures for managing Fuchs endothelial corneal dystrophy

Procedure	Indication	Feature
PKP	Late-stage FECD with corneal scarring	Replacing all layers of the cornea with a full-thickness corneal graft
DSEK	Mild or moderate FECD	Removing recipient's corneal endothelium and then transplanting donor's partial thickness corneal graft consisting of stroma, Descemet's membrane, and endothelium
		Also known as DSAEK as automated machine is usually utilized to prepare the graft
DMEK	Certain mild or moderate FECD	Removing recipient's corneal endothelium and then transplanting donor's partial thickness corneal graft consisting of Descemet's membrane and endothelium
DSO	Certain early-stage FECD	Removing centrally located dysfunctional endothelium without transplanting endothelium, allowing endothelium from the peripheral regions to migrate and repair the defects
		Also known as DWEK

FECD=Fuchs endothelial corneal dystrophy, PKP=Penetrating keratoplasty, DSEK=Descemet's stripping endothelial keratoplasty, DMEK=Descemet's membrane endothelial keratoplasty, DSO=Descemet's stripping only, DSAEK=Descemet's stripping automated endothelial keratoplasty, DWEK=Descemetorhexis without endothelial keratoplasty

performed as an improved procedure involving the removal of the dysfunctional corneal endothelium and transplantation of the donor's partial thickness corneal graft consisting of the stroma, Descemet's membrane, and functional endothelium, which can effectively prevent the cornea from accumulating excessive fluid.[20,21] With better clinical outcomes and fewer complications than PKP, DSEK is preferred in mild or moderate cases of FECD.[1,20,22] DMEK, a more precise and dedicated surgical method that involves a thinner graft with only the Descemet membrane and endothelium, was developed in the late 2000s.[21,23] Although this procedure requires advanced surgical skills, it further improves recovery and visual outcomes.[1,23] In recent years, DSO that features microscopic removal of centrally located dysfunctional endothelium has been developed, allowing the healthy endothelium of peripheral regions to migrate and repair defects.[24,25] DSO can be used in certain early-stage FECD with relatively intact peripheral endothelium.[24,25] In DSEK and DMEK, rejection and graft failure remain worrisome problems after surgery, in contrast to DSO, which requires no graft.[25]

Clinical Trials

To evaluate the latest trend of potential treatments for FECD, we searched for registered clinical trials and related research. Trials of potential treatments can be separated into two groups, the potential surgical treatment and the potential nonsurgical treatment.

Trials of surgical treatment

Currently, there are 32 surgery-associated clinical trials [Table 3] (seven trials are not shown since they only compare the results of existing surgical modalities). Among these trials, only two trials focus on the development of new surgical methods, including one trial exploring the effectiveness of acellular Descemet membrane transplant[26] and the other evaluates the potential of descemetorhexis in FECD patients.[27] On the other hand, new technologies to improve current surgical methods are common trial topics.[28,29,35] In one trial, researchers compared recovery and visual outcomes between femtolaser-assisted keratoplasty and conventional keratoplasty in patients with various corneal diseases, including FECD.[28] Another trial compares the extent of DSAEK graft damage using two different corneal graft injectors, EndoGlide or EndoSerter, in patients with corneal decompensation secondary to FECD or other diseases.[29] Tissue engineering technology is also tested to produce the human corneal endothelium as grafts for surgery.[30] Meanwhile, numerous trials focus on evaluating predictive factors of surgical outcomes[44-48] or improving the outcomes of existing

Table 3: Clinical trials on surgical treatments for Fuchs endothelial corneal dystrophy in the current decade

Trial class	Number	Topic	Remark
Potential new surgery	NCT03275896	Effect of acellular Descemet's membrane transplant in FECD patients[26]	The result is pending
	NCT02206594	Effect of descemetorhexis in FECD patients[27]	The result is pending
New technology	NCT03619434	Comparison of patient recovery and visual outcome between femtolaser-assisted keratoplasty and conventional keratoplasty[28]	Femtolaser is an effective method for corneal incision. The result is pending
	NCT01791075	Comparison of graft damage caused by surgery between using Endoglide and Endoserter injector[29]	The result is pending
	NCT04319848	Safety and efficacy of engineered human corneal endothelium for surgery[30]	The result is pending
	NCT04258787	Efficacy of using OCT to quantify corneal edema and predict surgical outcomes[31]	The result is pending
New technology - intraoperative OCT	NCT02423161	Clinical efficacy of intraoperative OCT[32]	Previous case series showed intraoperative OCT might facilitate surgery. The result of the trial is pending
	NCT03763721	Comparison of patient outcomes between intraoperative OCT-guided DMEK and conventional DMEK[33]	The result is pending
	NCT02423213	Clinical efficacy of microscope-integrated intraoperative OCT[34]	The result is pending
Methods to enhance graft attachment	NCT02542644	The effect of ultra-high resolution OCT to assess surgical outcomes in FECD patients after surgery[35]	The ultra-high resolution OCT has the potential to detect small detachment of the graft after DMEK. The result is pending
	NCT03407755	Comparison of graft attachment after DMEK between using sulfur hexafluoride and air[36]	The result is pending
	NCT04387331	Effect of wearable sensor to assess the impact of head position after operation[37]	The result is pending
	NCT05399095	Comparison of graft attachment after DMEK between maintaining supine position for 1 day and 5 days[38]	The result is pending
Prevention of graft rejection	NCT02834260	Effect of subconjunctival injection of dexamethasone-releasing implant to prevent rejection for FECD patients after surgery[39]	Dropless immunosuppression is probable after low rejection risk PKP
	NCT01853696	Effect of different dosages and regimens of corticosteroid for FECD[40]	The effect of loteprednol etabonate 0.5% gel is comparable to prednisolone acetate 1% solution
	NCT03248037	Effect of netarsudil in reducing IOP after corticosteroid treatment[41]	Netarsudil produced no significant difference in reducing IOP
	NCT05716945	Effect of fluorometholone 0.1% to prevent rejection for FECD patients after surgery[42]	The result is pending
Prevention of infection	NCT04018417	Effect of storing graft with amphotericin B to prevent postsurgical infection[43]	The trial was withdrawn due to poor results of *in vitro* research
Predictive factors for surgical outcomes	NCT05531760	Predictive factors for graft detachment in patients post-DMEK[44]	The result is pending
	NCT04469933	Predictive factors for favorable results after DMEK[45]	The result is pending
	NCT02849808	Predictive factors for long-term cornea graft survival[46]	No noticeable improvement factors associated with in long-term graft survival were found
	NCT01979250	Surgical outcomes in FECD patients with cataracts[47]	The major limitation to visual recovery after DSAEK is anterior corneal pathology
	NCT05134480	Surgical outcomes using diabetic donor's grafts[48]	The result is pending
	NCT02875145	Surgical outcomes in FECD patients after cataract surgery[49]	The result is pending
	NCT04420429	Predicting DMEK outcomes by preoperative anterior chamber depth, angle parameters, axial length, and other corneal parameters[50]	There was an association between surgical failure after DMEK and preoperative higher CCT values and lower ACD values

ACD=Anterior chamber depth, CCT=Central corneal thickness, DMEK=Descemet's membrane endothelial keratoplasty, DSAEK=Descemet's stripping automated endothelial keratoplasty, FECD=Fuchs endothelial corneal dystrophy, OCT=Optical coherence tomography, PKP=Penetrating keratoplas, IOP=Intraocular pressure

surgical methods.[49-57] These trials also explored whether previous cataract surgery affects the survival of the graft in patients with corneal diseases, including FECD.[49-57] In addition, the impact of different methods, such as the use of sulfur hexafluoride[36] and wearable sensors to record the post-surgical head position,[37] on enhancing graft attachment after DMEK has also been examined. In another trial, the graft attachment is measured to compare the benefit between maintaining the supine position for 1 day or 5 days after DMEK.[38] Currently, all of these trials are still in progress, requiring additional data collection and analysis before we can engage in an in-depth discussion.

Some clinical trials analyze ways to prevent rejection after corneal transplantation. Since FECD is not the only disease requiring transplantation, these trials mostly included patients with FECD and a few other corneal diseases. The subconjunctival injection of a dexamethasone-releasing implant is being investigated.[39] In a Phase 4, clinical trial focused on preventing graft rejection after DMEK, 233 eyes with corneal diseases, mainly FECD, were randomized to receive loteprednol, a newer class of corticosteroids, or prednisolone as part of their post-DMEK care.[58] The result showed no incidents of rejection in either the loteprednol or the prednisolone groups, suggesting that the anti-rejection effect of loteprednol was comparable to that of prednisolone.[40] However, topical corticosteroids may cause an increase in intraocular pressure (IOP).[40] To address this issue, a study was conducted using netarsudil, a Rho-associated kinase (ROCK) inhibitor, details of which will be elaborated later in this article.[41] The research involved patients who had undergone DMEK for corneal diseases, predominantly FECD. Participants were randomly assigned to the netarsudil group (95 eyes) or the placebo group (96 eyes).[41] The findings revealed no statistically significant differences between the netarsudil and placebo groups in terms of mitigating IOP elevation or preventing the loss of central corneal endothelial cells.[59] Postkeratoplasty infection is a rare but severe complication. A phase 2/3 study examines whether the addition of amphotericin B to the corneal storage solution can reduce the incidence of postkeratoplasty fungal keratitis, but the findings have not yet been published.[43]

Of all the new technologies to improve current surgical methods, it is worth mentioning that intraoperative OCT has recently been intensely studied. Intraoperative OCT generates high-resolution images of the ocular tissue, allowing surgeons to obtain detailed anatomy to improve surgical outcomes. The feasibility of intraoperative OCT has been investigated in two trials.[32,33] Since OCT is relatively large and operating rooms usually have limited space, it is difficult to implement intraoperative OCT in ordinary settings. Regarding structural limitation, one trial examined whether a new ophthalmology microscope with mounted OCT can improve the efficiency and results of surgery.[34] Nevertheless, none of the intraoperative OCT trials have yet reported their results.

Trials of potential nonsurgical treatment

To date, corneal transplants can provide FECD patients with favorable clinical outcomes. However, there are some limitations. For example, the sources of corneal graft are limited in most countries. Moreover, although the procedures of corneal transplantation are well established, complications after surgery remain concerning. Thus, nonsurgical treatments are becoming a focus in various studies and clinical trials in recent years. Potential nonsurgical treatment can be classified into three categories, which are pharmacological-associated treatment, cell therapy-associated treatment, and gene therapy-associated treatment.

Currently, there are 24 trials on potential nonsurgical treatment, of which 19 are treatments associated with pharmacology, 4 are treatments associated with cell therapy, and 1 is treatment associated with gene therapy.

Trials of potential pharmacology-associated treatment

There are 19 trials exploring pharmacological-associated treatment options for FECD [Table 4]. ROCK inhibitors are initially used to treat glaucoma, but their ability to increase adhesion, promote proliferation, and inhibit apoptosis of corneal endothelial cells have been demonstrated, making them potential treatments for other corneal endothelial disorders.[84,85] Clinical trials have been carried out to assess the potential benefits of adding ripasudil (Kowa Company Ltd, Nagoya, Japan), a ROCK inhibitor, to postoperative treatment since ripasudil was believed to accelerate postsurgical endothelial cell healing and elimination of corneal edema. However, the results of these trials are not available.[65-71] The efficacy of netarsudil, another ROCK inhibitor, in reducing corneal edema and central corneal thickness has been established in various trials.[62,64,86,87] Two clinical studies evaluating the therapeutic potential of netarsudil for treating FECD have published preliminary results.[62,64] In one study published by Lindstrom *et al.*, 40 patients with FECD were allocated to groups to receive netarsudil either once daily (QD) or twice daily (BID) for 8 weeks.[64] Both QD and BID regimens resulted in significant reductions of central corneal thickness at week 4.[64] Furthermore, from week 2 to week 8, the improvements in central corneal thickness and

Table 4: Clinical trials on nonsurgical treatments for Fuchs endothelial corneal dystrophy in the current decade

Treatment option	Stage	Number	Topic	Remark
Pharmacology-associated treatment				
ROCK inhibitor				
Netarsudil	Early phase 1	NCT04752020	Use of netarsudil in FECD patients after DSO[60]	ROCK inhibitors help increase adhesion, promote proliferation, and inhibit apoptosis of corneal endothelial cells, showing a promising area for further research
	Early phase 1	NCT04057053	Use of netarsudil in FECD patients with cataract after DSO[61]	
	Phase 2/3	NCT04051463	Effect of netarsudil on corneal edema in FECD patients[62]	
	Phase 2/3	NCT03971357	Effect of netarsudil on migration of corneal endothelial cells in FECD patients[63]	
	Phase 2	NCT04498169	Effect of different frequencies of netarsudil on corneal edema in FECD patients[64]	
Repasudil	Phase 2	NCT03575130	Effect of ripasudil in FECD patients after descemetorhexis[65]	
	Phase 2	NCT04250207	Effect of different doses of ripasudil in FECD patients after descemetorhexis[66]	
	Phase 2	NCT03813056	Effect of ripasudil in FECD patients after DMEK[67]	
	Phase 3	NCT05795699	Effect of ripasudil in FECD patients after descemetorhexis[68]	
	Phase 3	NCT05826353	Effect of ripasudil in FECD patients after simultaneous cataract surgery and descemetorhexis[69]	
	Phase 3	NCT05275972	Effect of ripasudil in FECD patients after DMEK and DSO[70]	
	Phase 4	NCT03249337	Effect of ripasudil in FECD patients after DSO[71]	
Elamipretide	Phase 1/2	NCT02653391	Effect of different doses of elamipretide in FECD patients[72]	Elamipretide is effective in restoring mitochondrial function
NAC	Phase 2	NCT04440280	Effect of NAC in FECD patients before DMEK[73]	NAC reduces the oxidative stress of corneal endothelial cells. The result is pending
Sirolimus				
STN1010904	Phase 2a	NCT05376176	Effect of different doses of STN1010904 in FECD patients[74]	STN1010904 suppresses the apoptosis of corneal endothelial cells. The result is pending
FGF1 analog				
TTHX1114	Phase 1/2	NCT04520321	Effect of different doses of TTHX1114 in FECD patients[75]	FGF1 analogs enhance cell proliferation and migration. The results are pending
	Phase 2	NCT04676737	Effect of TTHX1114 in combination with DSO in FECD patients[76]	
Hyperosmolar eye drops				
ODM5	RCT	NCT04140422	Effect of ODM 5 on morning corneal edema in FECD patients[77]	ODM5 is a hyperosmolar solution that supposedly can draw excess fluid from the cornea. The results showed no effect
	Observational	NCT02332109	Effect of ODM 5 on corneal edema in FECD patients[78]	
Cell therapy-associated treatment				
Magnetic corneal endothelial cells				
EO1404	Phase 1	NCT04191629	Clinical efficacy of EO1404 for corneal disease[79]	Magnetic corneal endothelial cells help direct cell therapies to the appropriate site.
EO2002	Phase 1	NCT04894110	Clinical efficacy of EO2002 for corneal disease[80]	

Contd...

Table 4: Contd...

Treatment option	Stage	Number	Topic	Remark
	Phase 1	NCT05636579	Clinical efficacy of EO2002 combined with ripasudil for corneal disease[81]	Evaluation of the safety and tolerability of these treatment options are still ongoing
Cultured human CEC	Nonrandomized, single group	UMIN000012534	Effect of cultured human CEC in combination with ROCK inhibitor[82]	Cultured human CEC with ROCK inhibitor is effective to restore patient's visual acuity
Genetic therapy-associated treatment				
QR-504a	Phase 1	NCT05052554	Clinical efficacy of QR-504a in FECD patients[83]	QR-504a normalizes mRNA splicing. The trial was aborted due to a lack of participants

CEC=Corneal endothelial cells, DMEK=Descemet's membrane endothelial keratoplasty, DSO=Descemet's stripping only, FECD=Fuchs endothelial corneal dystrophy, FGF1=Fibroblast growth factor 1, NAC=N-acetyl cysteine, RCT=Randomized controlled trial, ROCK=Rho-associated kinases

visual acuity were noticeable,[64] although there were no statistically significant differences between QD and BID groups.[64,86] In another study, Marianne *et al*. found that netarsudil could reduce corneal edema and improve visual acuity in patients with FECD.[62,87] Still, more research is required to explore the potential of netarsudil to delay or even obviate the need for surgical interventions in patients with ECD. Trials have also been conducted to evaluate the combined effects of netarsudil and surgical treatment as a therapeutic strategy for managing FECD, yet none of the results have been published to date.[60,61]

Other potential pharmacologically related treatments are also investigated. Elamipretide (Stealth BioTherapeutics Corp., Needham, MA, USA) is a mitochondrial protector that restores normal mitochondrial functions. It binds to the cardiolipin of the mitochondrial membrane, leading to the stabilization of the structure.[72] A trial is now underway to measure the efficacy and incidence of adverse events of elamipretide in FECD patients.[72] STN1010904 (Santen Pharmaceutical Co Ltd, Tokyo, Japan) is a product containing sirolimus. Acting as an mTOR inhibitor, STN1010904 suppresses corneal endothelial cell apoptosis and, therefore, decelerates the progression of FECD. An ongoing phase 2 clinical trial investigates its efficacy in patients with FECD.[74] N-acetyl cysteine (NAC) is an antioxidant and free radical scavenger. Proven in a mouse model with early-onset FECD, NAC reduces the oxidative stress of corneal endothelial cells.[73] Phase 2 research is ongoing to investigate the efficacy of NAC in patients with FECD.[73]

Fibroblast growth factor 1 (FGF1) is another promising therapeutic agent for corneal endothelial cell diseases because of its ability to improve cell proliferation and migration. However, native FGF1 loses its bioactivity rapidly, making it a less favorable option for regenerative therapy. TTHX1114 (Trefoil Therapeutics Inc, San Diego, CA, USA), an engineered form of FGF1, has a half-life longer than native FGF1.[88] Thus, TTHX1114 has great potential to treat FECD.[88] One clinical trial investigates the ability of TTHX1114 to treat FECD,[75] and another clinical trial tests its effects in patients post-DSO.[76] Both trials are ongoing.

Previously, several trials have tested using the osmotic effect to improve the visual acuity of FECD patients. There are two trials investigating the efficacy of ODM5 (Horus Pharma, Saint-Laurent-du-Var, France), a class of hyperosmolar eye drops, in FECD patients.[77,78] Zander *et al*. recruited FECD eyes with stromal edema, with 59 eyes receiving the hyperosmolar eye drop as treatment and 55 eyes receiving artificial tears as the placebo.[89] The result showed no clinically significant impact of hyperosmolar eye drops on early morning corneal edema.[89] In addition, many people (30 eyes) reported side effects, mainly a burning sensation after using hyperosmolar eye drops.[89]

Trials of potential cell therapy-associated treatment

Cell therapy is effective in replacing damaged cells or tissues. It can be used alone or in combination with other treatment modalities. In laboratory experiments and animal models, cultured human corneal endothelial tissue has shown promising results in restoring corneal physiology. It is specifically challenging to fix these therapeutic cells to the target location. EO1404 and EO2002 are two types of intracamerally injectable corneal endothelial cells. They are tagged by magnetic nanoparticles that help direct these cells to the target site, thus enhancing their regeneration effects.[90] To date, clinical trials are still being conducted to assess the safety and tolerability of these two cells [Table 4].[79-81] If EO2002 and EO1404 are proven effective, they will become easy and minimally invasive measures for treating corneal

endothelial disease without the need for transplant surgery. Hopefully, they may alleviate the problem that the supply of corneal grafts is limited.

In addition to isolated use, the combination of cell therapy with other treatment modalities is a promising approach for restoring corneal function. In a clinical trial, 11 bullous keratopathy eyes with no detectable corneal endothelial cells received an injection of cultured human corneal endothelial cells supplemented.[91] All 11 eyes exhibited a corneal endothelial cell density 24 weeks after injection.[91] This study revealed the potential of human corneal endothelial cell injection to restore normal corneal thickness, reduce in corneal edema, and improve in visual acuity.[91]

Trials of potential gene therapy-associated treatment

One pathogenesis pathway of FECD is the expansion of the CTG triplet in the TCF4 gene of chromosome 18.[92] The mutant TCF4 gene leads to failed pre-mRNA splicing and eventually causes endothelial cell death.[92] In one trial, the relationship between the number of triplet repetitions and the rate of FECD progression is analyzed.[93] Although this trial does not involve any new treatment, the result could potentially pave the way for personalized care and genetic treatment for FECD.[93]

In a study of cultured corneal endothelium, certain dead Cas9 (dCas9) molecules could reduce the expansion of the triplet of CTG in the TCF4 gene, making it a potential treatment option for FECD [Table 4].[94] Another potential treatment is intravitreal injection of QR-504a, which binds to the mutant portion of the TCF4 gene, resulting in the normalization of the mRNA splicing process.[83] In a trial [Table 4], the researcher aimed to evaluate the effect of QR-504a in patients with FECD.[83] However, this trial was aborted due to a lack of participants.[83] Future research is still needed to evaluate the efficacy of *in vivo* use of QR-504a and dCas9.

Proposed Algorithm

With more novel therapeutic approaches being developed in clinical trials, surgery may not remain the only standard for treating FECD. The proposed stepwise algorithm to improve the management of FECD is shown in Figure 2.

In general, nonsurgical measures should be used as first-line treatments for patients with mild FECD. Since pharmacological-associated treatments are simple and noninvasive, topical medications such as ROCK inhibitors, mTOR inhibitors, elamipretide, FGF1 analogs, or antioxidants are potential options to reduce corneal edema and improve visual acuity. Injectable corneal endothelial cells, such as EO1404 or EO2002, and injectable dCas9 molecules, such as QR-504a, are minimally invasive methods to restore normal functions of the corneal endothelium and, therefore, can serve as second-line treatments for FECD. Surgery, on the other hand, is reserved for patients with severe FECD or refractory to noninvasive or minimally invasive treatments. In addition to a single treatment, the combination of different therapeutic methods should also be considered, although more studies are required

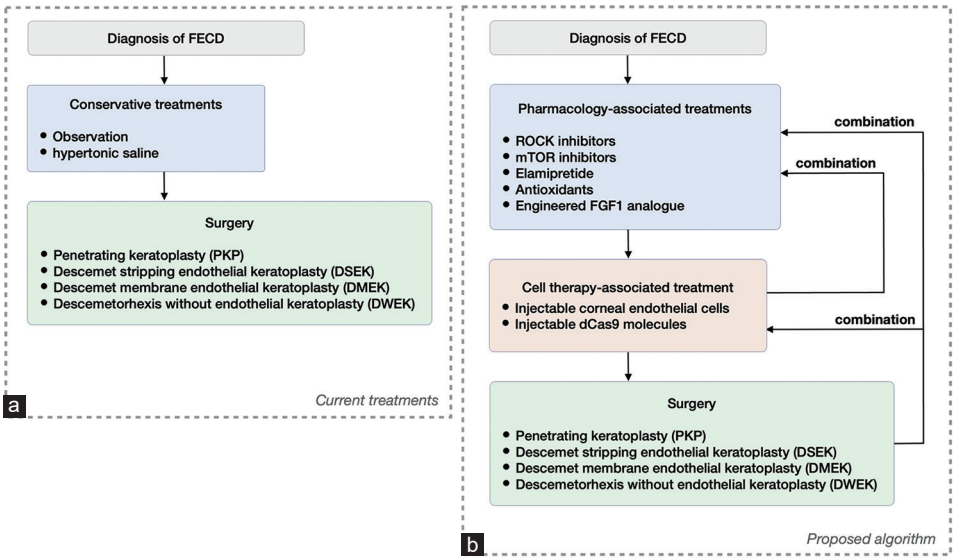

Figure 2: Algorithms for treating FECD. (a) Currently, only few conservative therapies could be tried. Surgery is the only definitive treatment for FECD. (b) As more novel therapeutic approaches are becoming available, a stepwise algorithm for treating FECD will substitute current surgery-centred manner. For patients with mild FECD, pharmacology-associated treatments should be used as the first line. Cell therapy-associated treatments are minimally invasive, being good candidates as second-line treatments. Surgery is reserved for patients with severe, refractory FECD. In addition to single treatment, the combination of different therapeutic methods should also be considered

to validate the efficacy of concurrent use of treatments with different mechanisms of action.

Notably, nonsurgical options may result in future complications requiring special attention. For example, in patients with medically well-controlled FECD, acute exacerbation of corneal edema may occur after lens replacement for cataracts, leading to severe and rapid loss of vision.[95] Thus, it is important for clinicians to consider various factors, such as comorbid ocular conditions, before choosing appropriate treatments.

Conclusions

In summary, FECD is a genetically and pathogenetically heterogeneous disease that commonly causes a decrease in vision. Currently, patients with FECD still rely on corneal transplantation as the definitive treatment. However, since corneal graft sources are limited and complications after corneal transplant are concerning, there is an unmet need for new treatment measures. As more trials are underway, we infer a stepwise algorithm will be a mainstay for treating FECD. For patients with mild FECD, nonsurgical or minimally invasive measures are used first. Surgery is reserved for patients with severe FECD. Although the results or data on the long-term outcomes of some studies are not yet available, it is still exciting that novel therapeutic approaches may be able to replace surgery as the only definitive treatment of FECD. Hopefully, the demand for corneal grafts will decrease with all the promising new measures.

Methods of Search

We conducted searches for FECD clinical trials on ClinicalTrials.gov and the UMIN Clinical Trials Registry using the terms "Fuchs corneal dystrophy," "Fuchs dystrophy," and "FECD." The study design, methods, and results of each clinical trial in the last 10 years were reviewed. In addition, we searched for related research on Embase and PubMed using the terms "Fuchs corneal dystrophy," "Fuchs dystrophy," and "FECD," along with keywords such as "treatment," "therapy," and "management." Articles related to FECD trials published within the last 10 years were reviewed. Data were collected between April 30th and May 5th, 2023.

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Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of Interest

The authors declare that there are no conflicts of interests of this paper.

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