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Descemet Endothelial Thickness Comparison Trial II (DETECT II): multicentre, outcome assessor-masked, placebo-controlled trial comparing Descemet membrane endothelial keratoplasty (DMEK) to Descemet stripping only (DSO) with adjunctive ripasudil for Fuchs dystrophy

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ABSTRACT

Introduction It remains uncertain whether Descemet membrane endothelial keratoplasty (DMEK) or Descemet stripping only (DSO) yields better outcomes in patients with symptomatic Fuchs endothelial corneal dystrophy (FECD). This paper presents the protocol for the Descemet Endothelial Thickness Comparison Trial II (DETECT II), a multicentre, outcome-masked, randomised, placebo-controlled, clinical trial comparing DMEK to DSO with ripasudil (DSO-R) for this patient population.

Methods and analysis A total of 60 patients with endothelial dysfunction due to symptomatic FECD will be enrolled from seven participating sites in the USA. The patients will be randomly assigned in a 1:1 ratio to one of the following treatment groups: group 1—DMEK plus topical placebo and group 2—DSO plus topical ripasudil 0.4%. The enrolment period is 24 months. The primary outcome is best spectacle-corrected visual acuity at 12 months. Secondary outcomes include peripheral and central endothelial cell density, visual acuity, vision-related quality of life and Pentacam Scheimpflug tomography. Study outcomes will be analysed using mixed effects linear regression. Adverse events, including rebubble procedures, endothelial failure and graft rejection, will be documented and analysed using appropriate statistical methods. DETECT II aims to provide evidence on the comparative effectiveness of DMEK and DSO-R. The results of this trial will contribute to optimising the treatment of FECD, while also exploring the cost-effectiveness of these interventions. Dissemination of findings through peer-reviewed publications and national/international meetings will facilitate knowledge translation and guide clinical practice in the field of corneal transplantation.

Ethics and dissemination A data and safety monitoring committee has been empanelled by the National Eye Institute. All study protocols will be subject to review and approval by WCG IRB as the single IRB of record. This study will comply with the National Institute

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although Descemet membrane endothelial keratoplasty (DMEK) has an excellent risk profile and visual outcomes and is currently the standard of care for primary endothelial disease. Descemet Stripping Only (DSO) with topical ripasudil may be a less invasive treatment for mild Fuchs endothelial corneal dystrophy patients without the long-term risks of graft rejection and graft failure associated with endothelial keratoplasty.

WHAT THIS STUDY ADDS

⇒ Here, we describe an National Institute of Health funded, multicentre, outcome-masked clinical trial randomising patients to (1) DMEK versus (2) DSO with adjuvant topical ripasudil 0.4%

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This should clarify differences in outcomes between these surgeries in mild Fuchs patients. Less invasive techniques such as DSO and medical therapies like ripasudil are attractive alternatives to traditional transplant and may ultimately be shown to be the treatment of choice in primary endothelial dysfunction.

of Health (NIH) Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. Data from the trial will be made available on reasonable request.

Trial registration number NCT05275972.

BACKGROUND

Although corneal transplantation has advanced over time, it still carries a risk of vision-threatening complications, such as graft rejection or graft failure, making less invasive therapies attractive. Descemet stripping only (DSO) may replace traditional keratoplasty in select patients. One small, open-label, randomised clinical trial (RCT) demonstrated faster recovery of visual acuity and more rapid endothelial cell migration in Fuchs endothelial corneal dystrophy (FECD) after DSO with adjunctive topical ripasudil (DSO-R).[1 2] Another non-randomised, prospective, interventional series found that 96% of patients with FECD achieved corneal clearance after DSO-R.[3]

The topically administered rho kinase (ROCK) inhibitor, ripasudil, may have an important role to play as an adjunctive treatment of endothelial disease. Ripasudil has been shown to protect against apoptosis and promote endothelial cell proliferation in vitro and in a human ex vivo model.[4–6] Other studies found ripasudil to upregulate genes and proteins related to the endothelial barrier, pump function in addition to cell cycle, adhesion and migration, and reduceimmune responses and suppressed proangiogenic factors leading to reduced graft rejection.[7 8] Clinical studies have supported these preclinical findings, particularly in the setting of DSO.[3] Therefore, adjuvant ripasudil may have a role to play in preventing progression in early FECD, and as an adjunctive treatment after surgical intervention.

DSO-R may be a less invasive treatment for mild FECD patients without the long-term risks of graft rejection and graft failure associated with endothelial keratoplasty. Here, we describe the methodology designed to investigate the role of DSO-R in the treatment of FECD.

Descemet Endothelial Thickness Comparison Trial II (DETECT II) is a National Institute of Health (NIH)-funded multicentre, outcome assessor-masked, placebo-controlled clinical trial randomising patients with symptomatic FECD to Descemet membrane endothelial keratoplasty (DMEK) versus DSO-R.[1] We anticipate that this trial will increase our understanding of which endothelial therapy results in better outcomes while minimising risks.

METHODS

Study design

The purpose of DETECT II is to determine differences in visual outcomes between DMEK versus DSO-R in symptomatic FECD. Patients (N=60) presenting to cornea clinics at participating sites with mild Fuchs endothelial dystrophy will be screened for inclusion. Those who consent to participate will be randomised in a 1:1 fashion to DMEK plus topical placebo versus DSO plus topical ripasudil 0.4% (online supplemental figure 1, full protocol available as online supplemental file 1).

Objective and hypothesis

The objective of this study is to determine whether DSO-R has superior postoperative best spectacle-corrected visual acuity (BSCVA) at 12 months compared with DMEK with a similar safety profile. We anticipate that DMEK will have better visual acuity compared with DSO during the early postoperative period of up to 3 months.

Study oversight

A data and safety monitoring committee (DSMC) has been empanelled by the National Eye Institute (NEI). This committee consists of five individuals and includes (a) cornea specialists, (b) an independent biostatistician, (c) a bioethicist and (d) representation from participating sites. The committee will meet twice per year for progress reports. Ad hoc meetings as needed may also be convened. Study investigators will conduct site visits annually. The principal investigators will notify the DSMC, study sites and institutional review boards of any changes to study protocols or any deviations from the trial protocols. Interim reports for the DSMC will be prepared by the data coordinating centre (DCC) at the F.I. Proctor Foundation (Proctor) at the University of California San Francisco (UCSF, San Francisco, California, USA). These reports will include (a) recruitment overall, and by study site, (b) compliance and (c) retention. The reports will also list study outcomes, and all adverse outcomes, including medication side effects, primary graft failure, graft rejection and mortality. The DSMC will determine the database closure dates for each report in advance; archival copies of the (a) main database and (b) study analysis files as they exist at the time of each report will be maintained. All reports will be sent using secure email to the members of the DSMC 2 weeks prior to each meeting.

Setting

Participants will be recruited from seven sites in the USA: Stanford University (Palo Alto, California, USA), Oregon Health & Science University (Portland, Oregon, USA), University of California Davis (Sacramento, California, USA), Dartmouth-Hitchcock Medical Center (Lebanon, New Hampshire, USA), University of Pennsylvania (Philadelphia, Pennsylvania, USA), University of Miami (Miami, Florida, USA) and Wills Eye Hospital (Philadelphia, Pennsylvania, USA). Participating surgeons are very experienced corneal surgeons who perform endothelial keratoplasty procedures on a weekly basis. They will be responsible for recruitment and enrolment, intervention implementation and follow-up visits. Surgeries could also be performed by cornea fellows who were being directly supervised by the attending physician. There are three resource centres. The Center for Ophthalmic Research & Novel Image Analysis at Stanford University will serve

as the clinical coordinating centre, the DCC will be at the F.I. Proctor Foundation at UCSF and the Cornea Image Analysis Reading Center (CIARC) at Case Western Reserve University will be the endothelial image analysis reading centre for the study. Stanford University will take the lead on the writing of study-related materials, writing journal publications and presentations. UCSF will take the lead on all data collection and analysis. The CIARC will serve as the central reading centre for the image analysis from eye bank and postoperative endothelial images to determine endothelial cell density (ECD), and the morphometric parameters (coefficient of variation (CV), % hexagonal cells (HEX)).

Eligibility

Inclusion criteria for this study include (1) being an appropriate candidate for either surgery, (2) having dysfunctional endothelium from FECD with confluent guttata not extending beyond 4.5 mm in diameter, (3) peripheral ECD of >1000 cells/mm^2, (4) being age 18 years or older, (5) willingness to participate in the study and follow-up visits and (6) willingness to consistently use study medications (ie, ROCK-inhibitors). Measurement of diameter of guttae, both horizontally and vertically, was performed at slit-lamp by surgeon with a dilated pupil and with the assistance of retro illumination.

Patients will be excluded if they have any of the following: (1) other primary endothelial dysfunction such as posterior polymorphous corneal dystrophy, (2) prior intraocular surgery other than cataract surgery or cataract surgery within the last 3 months, (3) >1 quadrant of stromal corneal vascularisation, (4) >3 clock hours of any anterior or posterior synechiae, (5) aphakia, anterior chamber intraocular lens (AC IOL), iris fixated IOL or scleral-fixated IOL in study eye prior to or anticipated during surgery, (6) fellow eye visual acuity worse than 20/200, (7) visually significant optic nerve or macular pathology, (8) inability to comply with postoperative instructions, (9) pregnancy or a desire to become pregnant, (10) hypotony (intraocular pressure <10 mm Hg), (11) preoperative central subepithelial or stromal scarring that the investigator believes is visually significant and could impact postoperative stromal clarity and visual acuity assessment and (12) more than one episode of anterior uveitis (eye must be quiet for at least 1 year prior to surgery).

Randomisation

Each study eye will be randomly assigned to one of the two treatment groups. Block randomisation stratified by site will be performed using a computer programme (Statistical package R; V.3.6; R Foundation for Statistical Computing, Vienna Austria) by the DCC. Once an eye is enrolled in the study, the study coordinator will assign the study participant's eye an ID (alpha-numeric code). A few days prior to surgery, the eye bank will randomise the available corneal tissue to determine which tissue will be used for the study. The eye bank will then look at the patient's treatment assignment and prepare the tissue if the patient is randomised to DMEK. The DCC will inform the surgeon of the study participant's randomisation assignment with regard to type of surgery.

Intervention

All patients randomised to DMEK will receive topical placebo and all patients randomised to DSO-R will receive topical ripasudil 0.4% postoperatively. Patients will begin topical medicines on postoperative day 1 and continue 4×/day for 3 months.

For the DMEK procedure, the tissue will be prepared by VisionGift (Portland OR) or Sierra Donor Services (Sacramento, Califonia, USA). Lenticule grafts will be prepeeled at the eye bank, prepunched to 7.0–7.5 mm (based on surgeon preference) and preloaded at the eye bank. The endothelium will be stained with trypan blue. The recipient Descemet's membrane will be stripped to 7.0–7.5 mm. A 2.4 mm corneal incision will be used, and the graft will be inserted with a modified Jones tube injector, micro Jones tube injector, LEITR glass cannula, micro Stephens glass cannula or Geuder cannula. The tap technique will be used to position the graft. Donor tissue or storage solution will be sent for fungal culture by the enrolment site. All study participants will receive a surgical peripheral iridotomy. DMEK grafts will be floated with a filtered air or 20% sulfur hexafluoride gas tamponade per surgeon preference.

For the DSO procedure, the pupil centre will be marked in mesopic conditions to guide centration. A 4.0 mm diameter imprint centred on the central mark will be used to guide the descemetorhexis. A reverse Sinskey hook or Gorovoy forcep will be used to gently initiate a tear in Descemet's membrane and Gorovoy DSO forceps (or similar instrument) will be used to complete the descemetorrhexis without disturbing the underlying stroma. The central Decemet's membrane and endothelium will then be gently peeled and removed with forceps. DSO-R patients will receive a small bubble of filtered air (approximately 4 mm diameter in supine position) injected for masking purposes.

All patients will be dilated postoperatively with 1% atropine and positioned supine for 24 hours. Subsequent supine positioning will be at the discretion of the surgeon. In the event of a need for a rebubble procedure, the surgeon will tell the patient that 'Descemet's membrane has detached' without mentioning if it is native Descemet membrane or the graft to preserve masking as much as possible. This study requires five visits to the clinic over a period of 2 years. There may be additional postoperative visits (above what the study requires) following this surgical procedure.

Medications will be purchased by the study and distributed to each enrolled patient individually by a partner pharmacy. We will obtain ripasudil 0.4% from Mimaki Family Pharmacy, Osaka, Japan and Japan Health (biojapan), Japan under IND #154317. All study participants will receive topical dexamethasone four times daily for

Table 1 DETECT II dosing schedule for medications

	Medication	Days 1–8	Days 9–30	Month 2	Month 3	Month 4	Month 5	Months 6–24
DSO-R	Ripasudil 0.4%	4×/day	4×/day	4×/day	4×/day			
	Dexamethasone 0.1%	4×/day	4×/day					
	(Dexamethasone) placebo			4×/day	4×/day	3×/day	2×/day	1×/day
	Ofloxacin	4×/day						
DMEK	(Ripasudil) placebo	4×/day	4×/day	4×/day	4×/day			
	Dexamethasone 0.1%	4×/day	4×/day	4×/day	4×/day	3×/day	2×/day	1×/day
	Ofloxacin	4×/day						

DETECT II, Descemet Endothelial Thickness Comparison Trial II; DMEK, Descemet membrane endothelial keratoplasty; DSO-R, Descemet stripping only with ripasudil.

1-month postoperatively. After 1 month, the DMEK group will continue dexamethasone 1% while the DSO-R group will be switched to placebo. Partner pharmacies will store and compound study medications: Rancho Park Compounding Pharmacy (for Stanford University, UC Davis, UM and OHSU); Penn Investigational Drug Services (for University of Pennsylvania) and Dartmouth Health Investigational Drug Services (for Dartmouth Hitchcock Medical Center). Study medication will be repackaged and relabeled into identical bottles and labels to preserve masking and the study participants will follow an identical tapering schedule as outlined in table 1.

Masking

All study participants will be masked to their intervention. Electronic medical records which are accessible to patients will be documented at the physician's discretion to prevent patient unmasking and participants are encouraged to not review their medical records. The visual acuity examiner performing the BSCVA will also be masked. Due to the nature of the surgical intervention, the surgeon performing study visit and the technician performing specular microscopy and other imaging may not be masked; however, all technicians at the clinic and image analysts at the CIARC will be masked.

Data collection and management

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility and timeliness of the data reported. Table 2 outlines the schedule of enrolment, interventions and assessments.

Clinical data (including adverse events, concomitant medications and expected adverse reaction data) and clinical laboratory data will be entered into Research Electronic Data Capture, a 21 CFR Part 11-compliant data capture system provided by the DCC at UCSF. These data will be kept confidential. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete or inaccurate.

Primary outcome and statistical analyses

The primary outcome for surgery type will be the 12-month BSCVA measured in logMAR using the Early Treatment Diabetic Retinopathy Study protocol. We will use a mixed effects linear regression model to evaluate BSCVA measured at 12 months with fixed effects for surgical treatment arm (expressed as a binary indicator variable for DMEK vs DSO-R), enrolment site and baseline BSCVA. We will include random effects for patients. The actual BSCVA at each time point will be used regardless of whether the patient had subsequent endothelial keratoplasty. We will tabulate results by study site. Permutation testing will be the basis of inference.

Secondary outcomes and statistical analyses

Endothelial cell density

We acknowledge that comparisons of ECD and cell loss between arms in this study are difficult because in one arm the endothelial cells are host cells and in the other, they are transplanted from a donor. However, we feel that gathering these data is important to further our understanding of the benefits and risks of these procedures. Three images will be obtained per eye at each time point and specified location. These images will be evaluated in a masked fashion at the CIARC. All images will be graded by two certified readers using the Konan centre method to determine ECD, the CV and the % HEX.[9–11] For quality control, a ≥5% difference in ECD determined by the 2 readers, or ≥15% differences in CV and % HEX, will be adjudicated by a third reader. We will analyse the difference in ECD at 6, 12, and 24 months in both central and peripheral locations.

- Central ECD: Our analysis will compare ECD between arms with a t-test at 6, 12 and 24 months. In the case of a non-normal distribution, we will use a Wilcoxon rank sum test. We will record and describe the cell loss over time in each group. Finally, we will analyse the relationship between 6-month ECD and subsequent requirement for a second endothelial procedure.
- Peripheral ECD: For both DMEK and DSO-R, baseline peripheral cell measurements will be recorded 4.5 mm from centre at 9 o'clock in the right eye

Table 2 Enrolment procedures for the Descemet Endothelial Thickness Comparison Trial II

Procedures	Screening pre-enrolment	Enrolment/ baseline, visit 1 day 0	Procedure, visit 2 day 5 (±14 days)	Follow-up, visit 3 month 3 (±1 month)	Follow-up, visit 4 month 6 (±1 month)	Follow-up, visit 5 month 12 (±2 months)	Final follow-up, visit 6 month 24 (±4 months)
Review inclusion/exclusion criteria	X						
Informed consent		X					
Demographics		X					
Medical history		X					
Randomisation			X*				
Administer study intervention			X				
Slit lamp examination		X		X	X	X	X
Intraocular pressure		X		X	X	X	X
Pachymetry		X		X	X	X	X
Pentacam topography and densitometry		X		X	X	X	X
Endothelial imaging†	X			X	X	X	X
Clinical photography‡		X			X		
BSCVA/ETDRS/MRx		X		X	X	X	X
Baseline form		X					
Follow-up form				X	X	X	X
Final form							X§
Visual function questionnaire		X		X		X	
Cost-effectiveness form							X
Interval history				X	X	X	X

*Randomisation performed by data coordinating centre approximately 1 week prior to surgery.
†Endothelial imaging may be completed at screening visit or enrolment visit, within 6 months of surgery.
‡Clinical photography also taken on adverse event.
§If participant does not complete the study, final form will be filled out at time of withdrawal or lost to follow-up.
.BSCVA, best spectacle-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; MRx, manifest refraction.

and 3 o'clock in the left eye using the Konan Cell-Chek 20 Plus (Konan Specular Microscope, Konan Medical, Irvine, California). Subsequent measurements at 6, 12 and 24 months will be captured in the same locations. These images will be quality assessed and archived. Subsequent grant funding will be obtained to further analyse these images. We will use a mixed effects linear regression model to evaluate % change in peripheral ECD measured at 6, 12 and 24 months with fixed effects for surgical treatment arm (expressed as a binary indicator variable for DMEK vs DSO-R) and enrolment site. We will include the patient as a random effect.

ECD at all time points

We will estimate the effect of surgery type on ECD in a repeated measures analysis including 6, 12 and 24 months using a linear mixed effects model with a random intercept for patient and fixed effects for clinical site, time and treatment assignment.

Endothelial cell morphology

We will use methods similar to the analysis for ECD to study the impact of DMEK versus DSO-R on the endothelial cell morphology by comparing the CV and variability in HEX shape. We will also analyse the relationship between higher CV and variability of HEX at 6 months and subsequent requirements for a second endothelial procedure.

Predictors of ECD

We will collect donor, recipient and operative factors that could potentially predict % ECD at 12 and 24 months, with particular interest in recipient and donor diagnosis of diabetes historically determined, donor age and operative complications. We will use LASSO regression with cross-validation to select the strongest predictors of ECD and will use a postselection correction to the SEs that account for the variable selection process.[12]

Visual acuity at other time points

We will estimate the effect of surgery on BSCVA at 3, 6 and 24 months using a linear mixed models for each time point, with random intercepts for patient and fixed effects for clinic site, baseline BSCVA and treatment assignment. In a subgroup analysis, we will analyse patients who require a secondary endothelial procedure.

Vision-related quality of life

Visual Function Questionnaire (VFQ) will be compared between groups using the NEI VFQ 25 (NEI-VFQ-25) at 3 and 12 months controlling for 1-day VFQ. This will be conducted using linear regression with baseline and assignment variables.

Pentacam Scheimpflug tomography

A rotating Scheimpflug camera will be used to provide three-dimensional images of the cornea. In addition to topographic maps with keratometric readings of the anterior and posterior cornea, OCULUS Pentacam reports on the total corneal power, corneal thickness maps, higher-order aberrations and densitometry. Statistical analysis will be similar to that describe above, linear mixed effects regression using treatment assignment and baseline values as covariates, using the same template as we did for BSCVA for the following variables:

- Higher-order aberrations: comparing the quantitative measure of irregular astigmatism, expressed in microns as the root mean square of the Zernike polynomials across the pupil (approximately central 4 mm of the pupil) controlling for baseline measurements.
- Densitometry: comparing a measure of corneal reflectance (ie, scarring) in grey scale units controlling for baseline measurements.
- Corneal thickness maps: comparing average central and peripheral thickness maps between surgeries at 3, 6, 12 and 24 months as patients heal from surgery.

Cost-effectiveness analysis

A supplementary analysis will use individual-level cost outcomes as well as individual-level health outcomes. We propose to report standard cost-effectiveness acceptability curves based on bootstrap resampling at the individual-level from both control and intervention subjects (for a statistical, clinical-trial-based, cost-effectiveness analysis from a healthcare system perspective).[13] The outcome variable will be the cost per line of vision gained.

Adverse events

All adverse events, including the number of rebubble procedures, secondary endothelial procedures, graft failure and graft rejection will be tabulated and reported. We will use the CTPS classification for graft failure and graft rejection.[14 15] Statistical comparisons will be conducted using Fisher's exact test, but with the caution that failure to find evidence of a difference cannot be used to infer a lack of risk difference for rare outcomes such as primary graft failure since the study is not powered to examine these.

Interim analysis

Interim reports for the DSMC will be prepared by the DCC. These reports will include (a) recruitment overall and by study site, (b) compliance and (c) retention. The reports will also list study outcomes and all adverse outcomes, including medication side effects, primary graft failure, graft rejection and mortality. Archival copies of the (a) main database and (b) study analysis files as they exist at the time of each report will be maintained. All reports will be sent using secure email to the members of the DSMC 2 weeks prior to each meeting. There are no formal interim stopping guidelines for the trial based on benefit, harm or futility, but every 3 months the DSMC will monitor serious adverse events for patient safety.

Sample size

With 30 patients per group (60 total), we estimate that we will have at least 90% power to detect a difference in logMAR of 0.1, assuming an outcome SD of 0.106, a two-sided alpha of 0.05 and 10% loss to follow-up. The SD was estimated from the DETECT pilot study and was adjusted for correlation between baseline and 12-month measurements (outcome SD=0.121, correlation=0.475, adjusted SD=0.106).

Dissemination plan

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial is registered at ClinicalTrials.gov, and the results from this trial will be submitted and published on ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals and to present these data at national and international meetings. Consistent with the collaborative nature of the proposed research, the principal investigator anticipates sharing all data generated by the study with collaborators. Analytical data sets that will be developed through the project will comply with the NIH Data Sharing Policy. The analytical data sets from this project will include patient-level data generated from the study visits. Data from the trial will be made available on reasonable request.

DISCUSSION

DETECT II aims to address several important knowledge gaps in the field of corneal transplantation. DMEK still carries a risk of complications such as the need for rebubble, graft failure and higher ECL.[16 17] DETECT-TES noted a higher rebubble rate and more rapid decline in central ECDs over time compared with UT-DSAEK although this was not statistically significant (12 months: UT-DSAEK, 2070±292 cells/mm2; DMEK, 1855±448 cells/mm2 (p=0.051)). A non-prespecified sensitivity analysis using repeated measures of ECDs from baseline to 24 months, and clustering by patient, showed ECL among DMEK was higher than UT-DSAEK (p=0.006). The long-term implications of ECL on graft survival are important and may have an impact on the donor pool as more surgeons adopt the technique.

One interesting ex vivo study of endothelial cells from patients with FECD undergoing corneal transplantation placed one-half of the stripped endothelial lamellae in media with ripasudil and the other half without. Ripasudil-treated endothelial cells expressed genes related to cell

cycle and stimulated cell proliferation. Ripasudil also upregulated genes related to cell adhesion and migration, and those involved in converting cells from a static to a motile phenotype. Perhaps most surprising was the fact that ripasudil-treated cells also had upregulated endothelial pump and barrier function for up to 72 hours after a single dose. Adjunctive ripasudil has the potential to protect against apoptosis and promote cell health and proliferation which may profoundly impact ECL and the need for corneal transplantation.[18]

DSO may be the treatment of choice for early symptomatic FECD and avoids the risk of graft rejection, failure or glaucoma associated with long-term topical steroid treatment. An open-label RCT randomised FECD patients to DSO-R versus DSO. Those randomised to DSO-R recovered vision of 20/40 or better approximately 2 weeks faster and had higher ECD at 6 months.[2] Another non-randomised, prospective interventional series found that 96% of visually significant FECD with guttata confined to central cornea and good peripheral cell counts had complete corneal clearing within 4 weeks with topical ripasudil 0.4%. Relapse oedema occurred in 39% but was completely cleared with recommencement of the drop, suggesting a drug effect.[3] These studies suggest that, in carefully selected patients, DSO-R may be a safer option which avoids many of the risks associated with DMEK. However, it is unknown how the visual acuity or time to another endothelial procedure compares between these two techniques. DETECT II will impact clinical practice regarding these therapies. It also has the potential to yield longer-term outcome data, although that is beyond the scope of this 5-year funding.

While DETECT II has certain limitations that should be acknowledged, the ideal ripasudil dose/duration is currently unknown. One trial evaluated 6×/day dosing until corneal clearing.[3] Four times daily for 3 months with a taper was chosen for this study to balance offering adequate treatment with costs while reducing the likelihood of toxicity. Additionally, while it is a compelling thought to treat DMEK patient with topical ripasudil, this question is being evaluated in DETECT I.[1] This design allows us to test DSO-R against the standard of care for endothelial disease which is currently DMEK.

In conclusion, the DETECT II trial is poised to contribute significantly to the knowledge base of corneal transplantation by evaluating the effectiveness of DMEK and DSO-R. Endothelial keratoplasty is currently the treatment of choice for corneal endothelial disease. Less invasive techniques such as DSO and medical therapies like ripasudil are attractive alternatives to traditional transplant and may ultimately be shown to be the treatment of choice in primary endothelial dysfunction. We anticipate that this study will greatly increase our understanding of which patients with endothelial disease, in particular, with FECD, will benefit from DMEK versus DSO-R. We also anticipate that we will improve our understanding of the peripheral endothelium in disease states such as FECD. The outcomes of this trial, along with other ongoing studies and advancements in the field, will shape the future of corneal transplantation while minimising complications.

Trial status

This protocol is version December 2023. Recruitment began in September 2023 and is expected to last until approximately September 2026.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

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Contributors CCL, WC, BHJ, BFA, TML and JR-N were involved in study design. CCL, WC, BHJ, BFA, JYL, WG, NV, SA and JR-N were involved in study implementation. All authors reviewed and edited the paper. BFA and JR-N took responsibility for integrity of the data. Guarantors: JR-N and BFA.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and WCG IRB serves as the Single IRB of Record for DETECT. The IRB tracking number is: 20220590. Participants gave informed consent to participate in the study before taking part.

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