STUDY PROTOCOL

PROTOCOL TITLE:
Evaluation of the Efficacy of Descemet membrane transplantation for the Treatment of Fuchs' Endothelial Dystrophy

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PROTOCOL SIGNATURE PAGE

Protocol Title: Evaluation of the Safety and Efficacy of Descemetoplasty for the Treatment of Fuchs' Endothelial Dystrophy

Protocol Number: R1366/52/2016

Protocol Version/ Date: 3.0 / 28 August 2017

Sponsor Name: NA

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and Singapore Guideline for Good Clinical Practice (SGGCP).

Principal Investigator Name: _____

Principal Investigator Signature: _____

Date: _____

1. BACKGROUND AND RATIONALE

The cornea maintains structural integrity of the eye while providing an optically clear interface through which light may be refracted. Anatomically, it may be divided into 3 layers – epithelium, stroma and endothelium. The stroma comprises multiple layers of collagen within a matrix of water and glycosaminoglycans, while the underlying endothelium regulates stromal hydration to ensure corneal clarity.

Fuchs Endothelial Dystrophy (FED) is a degenerative disease affecting the corneal endothelium, characterized clinically by guttate excrescences on the posterior corneal surface and dysfunctional corneal endothelial cells. While patients are commonly asymptomatic in their early stages, advanced FED can be associated with significant corneal edema, scarring and impairment of visual function.

Prevalence of FED in the local Chinese population has been estimated to be in the range of 8.5% for females and 4.4% for males.[1] Genetic susceptibility to FED may be explained by the presence of genetic anomalies such as the CTG18.1 repeat expansion[2], TCF4 single nucleotide polymorphisms[3] and SLC4A11 point mutations[4], amongst many others.

Patients with mild FED are usually managed conservatively with the application of topical hypertonic saline eyedrops. For patients with advanced FED, endothelial keratoplasty may often be necessary. In 2014, FED represented the most common indication for endothelial keratoplasty in the United States, accounting for 47.7% (13,817 cases) of all endothelial keratoplasty procedures performed nationwide[5]. In Singapore, FED was the second most common indication for corneal transplantation.

Endothelial keratoplasty is associated with endothelial cell attrition in the range of 29.7%[6] – 47% by the 3rd post-operative year. Additionally, the global demand for corneal graft material currently still far outstrips supply,[7,8] critically limiting the number of patients who can potentially benefit from these surgical interventions. As such, there is a need explore alternative, sustainable strategies for the management of FED.

In 2009, Shah et al. reported the treatment of a 34 years old patient, with the combined pathologies of FED and Posterior Polymorphous Corneal Dystrophy (PPMD), by primary stripping of the central 4-5mm of Descemet's membrane without corneal graft transplantation ('Primary Descemetorhexis').[9] Contrary to conventional expectations, there was complete repopulation of the posterior corneal surface by corneal endothelial cells following the surgery, with best-corrected-visual-acuity (BCVA) of 6/7.5 achieved by the 6th post-operative month. In 2014, Moloney et al. published a similar report of a 54 years old patient, diagnosed with FED, successfully treated by Primary Descemetorhexis.[10] Rapid endothelial recovery, as evidenced by a central endothelial cell count of 620 cells/mm^2 and BCVA of 6/6, was achieved by approximately 6 weeks after the surgery. The success of these cases raised the prospect of Primary Descemetorhexis as a feasible alternative for the treatment of FED.

However, these anecdotal accounts must be balanced by a significant number of other

seemingly contradictory reports. For example, in 2013, Bleyen et al. reported in a prospective clinical trial of 8 patients who underwent primary descemetorhexis for the treatment of FED, that 7 of them eventually required rescue endothelial keratoplasty (DM transplant with Endothelial cells) in view of poor vision secondary to corneal edema.[11] FED patients treated by primary descemetorhexis (central 6 – 6.5mm) without endothelial graft were also reported by Arbelaez et al. to be dissatisfied with their visual outcomes secondary to reasons such as slow visual recovery and visual disturbances secondary to persistent stromal edema and scarring[12].

To gain a better understanding of the factors which may affect endothelial recovery following Primary Descemetorhexis, we performed an ex vivo human corneal endothelial cell culture experiment in which Primary Descemetorhexis was performed on cadaveric human cornea buttons, followed by ex vivo culture for a duration of 2 weeks to allow for endothelial recovery. A less invasive approach of denuding endothelial cells from the Descemet's membrane (DM), while maintaining anatomical integrity of the DM, was also assessed. We found that advanced patient age and the absence of DM were significantly associated with slower endothelial recovery.[13]

As such, we hypothesized that the outcomes of Primary Descemetorhexis for the treatment of FED may be improved by DM transplantation following Primary Descemetorhexis ('DM Transplantation'). The main difference between our proposed technique of DM transplantation and conventional endothelial keratoplasty is that the DM transplant does not require the presence of a functional corneal endothelial monolayer on the graft. If successful, the greatest advantage of this approach would be to greatly expand the pool of donors who are eligible to provide cadaveric corneal graft tissue for transplantation. This also opens up the possibilities of designing synthetic DM materials in the future.

References

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2. HYPOTHESIS AND OBJECTIVES

Hypothesis

Stripping of Descemet's membrane, followed by transplantation of a donor Descemet's membrane graft (i.e. 'DM transplant'), is an effective alternative to endothelial keratoplasty for the treatment of Fuchs' Endothelial Dystrophy.

Specific objectives

1. Primary aim: To evaluate the speed and extent of endothelial recovery and visual rehabilitation following DM transplant for the treatment of FED
2. Secondary aim 1: To evaluate the long term stability of post-operative outcomes of DM transplant, in terms of both endothelial cell count and best-corrected-visual-acuity, for the treatment of FED
3. Secondary aim 2: To evaluate the effect of Rho kinase inhibitor on the speed and extent of endothelial recovery and visual rehabilitation following DM transplant for the treatment of FED in patients above the age of 65. .

3. EXPECTED RIKS AND BENEFITS

Reported complications rates in Endothelial Keratoplasty are low. DM is expected to be associated with comparable complication rates. Complications may occur either intra-operatively or post-operatively[1]:

Intra-operative complications:

- Incomplete stripping of host Descemet's Membrane (DM): 1.6%
- Air bubble-related problem: 1.3%
- Scoring and stripping of host DM not possible: 0.9%
- Reverse-unfolding of donor DM: 0.5%
- Inadvertent expulsion of donor button from anterior chamber: 0.2%

Post-operative complications:

- Donor graft dislocation: 4.9%
- Air-bubbled induced pupillary block glaucoma: 2.8%

- Secondary glaucoma: 1.6%
- Partial donor graft detachment: 0.7%
- Delayed visual rehabilitation from primary failure 5%
- Blood in graft interface: 0.5%
- Bacterial endophthalmitis: 0.2%

Benefits:

- Endothelial keratoplasty is currently the standard of care for the management of advanced Fuchs' Endothelial Dystrophy
- The patient may benefit since the endothelial recovery will be from their own cells and not donor cell, hence there will no risk of rejection
- Since the cell will be from the patients own, the long term endothelial cell attrition seen in current endothelial keratoplasty techniques will not occur
- Since the cells will the patients own their will be no need to use prolonged topical immunosuppression and hence avoid the risk of steroid related complications e.g. glaucoma
- The patient's participation will contribute to the medical knowledge about the use of DM transplant for the treatment of Fuchs' Endothelial Dystrophy.

Risks

- The endothelial recovery may be prolonged – if this occurs then the patient will be given the option to undergo a conventional endothelial keratoplasty

References

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4. STUDY POPULATION

4.1. Number and nature of subjects to be enrolled.

Patients will be recruited at Singapore National Eye Centre. The study will be a prospective, open label clinical trial where **20 patients** will be selected to undergo DM transplant for the treatment of Fuchs' Endothelial Dystrophy (FED).

The patient population for this study is patients with FED. Our previous ex vivo study has shown that older patients (>65 years old) are less likely to respond favourably to DM transplant alone and data from reported clinical cases of DM stripping alone have shown that endothelial recovery was only achievable in 50% of the cases over the age of 65 years old. Hence, an age range of <65 years old is set for this study. To include age range >65 to 85 as well, Rho kinase inhibitor eye drops will be prescribed to patients with age higher than 65 years old. 10 patients age between 65 to 85 will be recruited for DM transplant coupled with Rho kinase inhibitor. No racial, minority or gender exclusion criteria will be applied.

4.2. Criteria for Recruitment and Recruitment Process

Patients with Fuchs' Endothelial Dystrophy who are interested in participating and have provided informed consent will be examined preoperatively by the principal investigator (A/Prof Jodhbir Singh Mehta). Baseline measurements to assess eligibility will include age, slit lamp assessment, slit lamp photography, intraocular pressure, specular microscopy, ultrasound corneal pachymetry, Pentacam scan, best corrected visual acuity, contrast sensitivity and anterior segment colour photography. These tests will be performed by certified ophthalmic imaging technicians and Singapore Nursing Board registered staff nurses employed by the Singapore National Eye Centre. A random venous blood sample will also be obtained from each patient and subject to genetic analysis for the presence of the CTG18.1 repeat expansion. Venepuncture will be performed by a Singapore Nursing Board registered staff nurse employed by the Singapore National Eye Centre.

The decision for eligibility for recruitment into the study will be made by the principal investigator (A/Prof Jodhbir Singh Mehta), based on results of the pre-operative assessment. Informed consent and pre-operative counselling will be administered by a specialized research coordinator employed by the Singapore National Eye centre / Singapore Eye Research Institute. The principal investigator (A/Prof Jodhbir Singh Mehta) will be available to provide clarifications and explanations if requested by the participant or research coordinator.

4.3. Inclusion Criteria

1. Fuchs' Endothelial Dystrophy (FED) as defined by any of the following criteria:
    a. FED of at least Grade 4 on the Krachmer grading scale (i.e. greater than 5mm of confluent central corneal guttata)
    b. Best-corrected-visual-acuity of less than 6/12 in a patient clinically diagnosed with FED of any grade, in which poor visual acuity cannot be accounted by any other significant ophthalmic disease (e.g. cataracts, age-related macular degeneration, glaucoma, optic neuropathies)
2. Patients in the range of <85 years old will be recruited for this study
3. Only individuals with the mental capacity to provide informed consent will be included.
4. Patients who are willing and able to sign a written Informed Consent Form prior to any study-specific procedures will be included
5. Patients who are willing and able to return for scheduled follow-up examinations for up to 12 months after the surgery will be included

4.4. Exclusion Criteria

Subjects that meet any of the following criteria will be excluded from participation:

1. Eyes which have previously been subject to any form of keratoplasty
2. An only-functioning eye in a patient who has lost visual potential in the contralateral eye
3. Patients with chronic, advanced FED who meet the above mentioned inclusion criteria, but whose disease is associated with significant stromal scarring to such an extent that will predictably impair post-operative visual recovery after DSAEK or DM transplant
4. Patients whose corneal endothelial disease may possibly be attributed to pathologies

other than FED, including but not limited to pseudophakic bullous keratopathy, laser-peripheral-iridotomy induced bullous keratopathy, iridocorneal endothelial syndrome, Axenfeld Rieger syndrome, congenital hereditary endothelial dystrophy and any other anterior segment developmental anomalies

5. Patients with visually significant cataracts
6. Patients with diagnosed with visually significant retinal disease, including but not limited to age-related macular degeneration, myopic macular degeneration, diabetic retinopathy, diabetes related maculopathy, retinal vein occlusion related maculpathy, retinal dystrophies and previous retinal detachments.
7. Patients with any form of glaucoma
8. Patients diagnosed with visually significant, non-glaucomatous optic neuropathies, including but not limited to those related to ischemic (both arteritic and non-arteritic), toxic, nutritional, myopic, compression, infective and inflammatory causes
9. Patients who are pregnant, lactating, of child-bearing potential and not practising a medically approved method of birth control, or planning to become pregnant during the course of the trial, and patients with other conditions associated with fluctuation of hormones that could lead to refractive changes.

5. STUDY DESIGN AND PROCEDURES/METHODOLOGY

Study Design

This is prospective, open non-randomized clinical trial. Eligible patients who fit our recruitment criteria and who are interested in surgery for improvement of symptoms related to FED will be informed of the availability of this study at the Singapore National Eye Centre. They will first be counselled on the procedures involved in conventional endothelial keratoplasty, which is the current standard of care, together with a discussion on the risks and benefits associated with endothelial keratoplasty. They will subsequently be presented with the alternative option of DM transplant, with a full explanation detailing the experimental nature of this approach, together with a discussion on the potential risks and benefits of DM transplant vis-à-vis conventional endothelial keratoplasty. They will also be counselled regarding the possibility of subsequently undergoing a rescue endothelial keratoplasty procedure in the post-operative period, should there be evidence suggesting that there is prolonged visual recovery following DM transplantation. Patients will be informed of the potential risks and benefits of the rescue endothelial keratoplasty. After provisional consent, patients will be screened for inclusion and exclusion criteria (listed above). Patients that meet the eligibility criteria will be consented and assigned to undergo DM transplant in the eye that has the more severely affected by FED. We aim to recruit a total of **20** patients for this study.

Graft Preparation

Donor corneas will be supplied by the Singapore Eye Bank. A 5-6mm Descemet's membrane graft will be prepared from the corneal button. Endothelial cells will be removed by simple wiping with a spear and removal of endothelial cells will be confirmed by trypan blue staining. All preparation will be performed by the principal investigator (A/Prof Jodhbir Singh Mehta), with the assistance of accredited technicians at the Singapore Eye Bank.

Surgical Procedure

All DM transplant procedures will be performed at the Singapore National Eye Centre (SNEC) by a fully qualified corneal surgeon (A/Prof Jodhbir Singh Mehta, Head of the corneal service) who regularly performs and teaches endothelial keratoplasty. The surgical procedure will involve 1) Corneal incision, 2) Stripping of the central 5-6mm diameter of host diseased Descemet's membrane and endothelium, 3) Insertion of donor Descemet's roll, 4) Unscrolling of Descemet's membrane graft and positioning onto the posterior corneal surface by an expansile gas bubble (20% Sulphur Hexafluoride, SF_6), 5) Creation of an inferior peripheral iridotomy, and 6) Closure of corneal incision with 10-0 nylon sutures.

Post-operative Care

All patients will be prescribed topical antibiotics and steroidal eyedrops post-operatively. For patients above the age of 65, an additional Rho kinase inhibitor eyedrop will be prescribed to the patient. They will be reviewed by the surgeon (A/Prof Jodhbir Singh Mehta) immediately after the procedure, at post-operative day 1, week 1, week 3, week 6, week 12, week 24 and week 48. Additional visits may be scheduled as required.

Primary outcomes

Measurements of best-corrected-visual-acuity, central endothelial cell count and corneal pachymetry will be obtained every month, starting from post-operative month 1. These measurements will be made by certified ophthalmic imaging technicians and Singapore Nursing Board registered staff nurses employed by the Singapore National Eye Centre.

Other outcome Measurements

1. Slit lamp examination every visit to visualize graft position and corneal hydration status
2. Intraocular measurement with Goldmann applanation tonometry every visit
3. Anterior segment optical coherence tomography (ASOCT): Non-invasive non-contact measurement with Optical Coherence Topography, Visante (day 0, day 1, week 1, month 1 and month 12)
4. Pentacam scan: Non-invasive non-contact scan with OCULUS Pentacam (day 0, month 3 and month 12)
5. Documentation of any postoperative complications including but not limited to wound leak, graft dislocation, partial graft detachment, SF_6-bubble induced pupillary block glaucoma, iris damage and bacterial endophthalmitis

All measurements will be made by the principal investigator (A/Prof Jodhbir Singh Mehta), certified ophthalmic imaging technicians and Singapore Nursing Board registered staff nurses employed by the Singapore National Eye Centre.

Rescue Endothelial Keratoplasty

Post-operatively, patients who have undergone DM transplant will be clinically assessed by the surgeon (A/Prof Jodhbir Singh Mehta) during each post-operative visit. Prolonged visual recovery defined as clinical outcomes which are significantly worse than what would be expected following conventional endothelial keratoplasty for the treatment of FED in an equivalent patient i.e no improvement in visual acuity by 6 weeks. A patient who demonstrates poor recovery, or non-recovery, may be counselled on the need for rescue

conventional endothelial keratoplasty procedure, as determined by the surgeon (JSM). The patient will be advised on the procedures involved, and the associated risks and benefits. Patients who consent to rescue endothelial keratoplasty will undergo standard Descemet's Stripping Automated Endothelial Keratoplasty (DSAEK) performed by the surgeon (A/Prof Jodhbir Singh Mehta) at the earliest possible date.

Data Collection and Storage

The surgical procedure will be recorded on a DVD. The DVD will be stored in a locked cupboard and retained for 15 years; it will be put in long-term storage afterwards. All the data from imaging procedures will be stored on password-protected devices at Singapore National Eye Centre. All other clinical examination data will be entered and stored in confidential patient dossiers maintained by the Medical Records Office of the Singapore National Eye Centre at a secure location within the Centre. Data and samples may be de-identified and used for future studies. Where required, such future studies will be submitted for review and necessary approval by the relevant institutional review board.

Withdrawal

Subjects may withdraw voluntarily from participation in the study at any time. If they withdraw from the study after consenting but prior to surgery, no specific arrangements for follow-up or special care are required. If they withdraw from the study in the follow-up period, after having surgery, they will be advised to continue the regular scheduled follow-up for safety reasons. If a patient withdraws from the study due to the development of a complication, appropriate follow-up will be arranged until the symptoms of the adverse event resolve and the subject's condition becomes stable.

6. SAFETY MEASUREMENTS

6.1. Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect
- is a medical event that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

6.2. Collecting, Recording and Reporting of Adverse Events and Serious Adverse Events to CIRB

All adverse events will be reported via submission of the completed SAE Reporting Form to the approving CIRB, by the PI, within the timeframe defined below. The PI will also be responsible for informing the institution representative (local SAE resulting in death), sponsor or regulatory bodies as required and appropriate.

Reporting timeline to CIRB:

- SAE that result in death, regardless of causality, will be reported immediately – within 24 hours of the PI becoming aware of the event.
- Local life-threatening (unexpected/ expected) SAE will be reported no later than 7 calendar days after the PI is aware of the event, followed by a complete report within 8 additional calendar days.
- Local unexpected SAE that are related events, but not life-threatening, will be reported no later than 15 calendar days after the PI is aware of the event.
- An increase in the rate of occurrence of local expected SAE, which is judged to be clinically important, will be reported within 15 calendar days after the PI is aware of the event.
- Local expected SAE will be reported annually (together with Study Status Report for annual review).
- Local unexpected and unlikely related SAE that are not life-threatening will also be reported annually (together with Study Status Report for annual review).
- Local unexpected AE that are related events will be reported at least annually (together with Study Status Report for annual review).
- Non-local unexpected SAE that are fatal or life threatening and definitely/probably/possibly related will be reported not later than 30 calendar days after the PI is aware of the event.

6.3. Safety Monitoring Plan

Efficacy is assessed every 3 months. Any SAE every 1 month, any AE 3 monthly.

6.4. Complaint Handling

Each research participant is accorded similar rights as per any other clinical SNEC patient. All complaints will first be directed towards the PI via the quality services department. If necessary, the complaint will be escalated to the head of service and subsequently, the medical director.

7. DATA ANALYSIS

7.1. Data Quality Assurance

Data entry will be performed by a minimum of 2 personnel, one of which will cross-check the accuracy of data entered by the other.

7.2. Data Entry and Storage

Data will be entered on a Microsoft Office Excel spreadsheet and kept secure with password protection. Only members of the research team will have access to the data.

8. SAMPLE SIZE AND STATISTICAL METHODS

8.1. Determination of Sample Size

This is an exploratory, first-in-man study of DM transplant for the treatment of FED. Although preclinical laboratory studies have provided evidence to suggest the feasibility of DM transplant, there are no previously published clinical data pertaining to its efficacy in humans. As such, we have restricted recruitment of participants for this study to a total number of **20**.

8.2. Statistical and Analytical Plans

a. General Considerations: The collected data will be analysed with the Statistical Package for Social Sciences (SPSS).
b. Safety Analyses: Data regarding safety will be analysed monthly.
c. Interim analysis: Interim analyses done when 25%, 50%, and 75% patients have completed their "3-month" follow-up

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The trial coordinator and the principal investigator will be responsible for the evaluation of adherence to protocol, data quality and this review will be carried out monthly.

11. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Singapore Good Clinical Practice and the applicable regulatory requirements.

This final study protocol, including the final version of the Patient Information and Informed Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB), prior to enrolment of any patient into the study.

The principal investigator is responsible for informing the CIRB of any amendments to the protocol or other study-related documents, as per local requirement.

11.1. Informed Consent

Only patients with good mental capacity will be recruited. Counselling will be carried out by the principal investigator, research team, and research nurses. Specific patient information and informed

consent documentation will be used and these will be stored in the patient records. Consent will be obtained prior to the day of surgery. The investigator will comply with the SGGCP guidelines and to the ethical principles that have their origin in the Declaration of Helsinki.

11.2. Confidentiality of Data and Patient Records

Patient data on the spreadsheet will be anonymous with coding. Data will be stored on password-protected computers. All blood samples collected will be labelled with the anonymous code corresponding to the patient's identity. All activities related to the collection, use and disclosure of personal patient data will be performed in accordance to the requirements set out under the Singapore Personal Data Protection Act (PDPA) 2012.

12. PUBLICATIONS

Publication authorship, acknowledgments, and review procedures for scientific publications will be determined by the principal investigator.

13. RETENTION OF STUDY DOCUMENTS

Records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.) as well as IRB records and other regulatory documentation will be retained by the PI in a secure storage facility. The records will be accessible for inspection and copying by authorized authorities. Study documents will be kept by SERI for 15 years, and then destroyed.

14. FUNDING and INSURANCE

This study is department supported.

The cost of Descemet Membrane Transplantation surgery and genetic analysis of CTG trinucleotide repeats will be absorbed by the department. Participants will pay for all other costs including all pre- and post-operative follow-up visits, and all relevant investigations performed. The clinical visit schedule and investigations required are identical to patients undergoing standard endothelial keratoplasty, thus participants will not be required to pay more than what is expected for standard endothelial keratoplasty.

Should a complication occur, the follow-up treatment will be to perform a standard endothelial keratoplasty, and the participant will be expected to bear the cost of this surgery i.e. such a participant will pay the same surgical fees as a conventional patient who decides to undergo standard endothelial keratoplasty for treatment of Fuchs Endothelial Dystrophy.

Singapore National Eye Centre and Singapore Health Services do not make any provisions to compensate study participants for research related injury or complications. However, compensation may be considered on a case-by-case basis for unexpected complications and injuries due to non-negligent causes.