ISRCTN54055321 https://doi.org/10.1186/ISRCTN54055321

Ex vivo expanded corneal limbal stem cell transplantation

Submission date
15/03/2012

Recruitment status
No longer recruiting

Registration date
28/03/2012

Overall study status
Completed

Last Edited
06/03/2018

Condition category
Eye Diseases

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English Summary
Background and study aims
The cornea is the clear front of the eye, and its transparency is vital to allow you to see properly. Special cells called limbal stem cells, at the edge of the cornea, are responsible for repairing any damage and keeping the cornea healthy and clear. If the cornea is very badly damaged or if there arent enough of these special cells, this can result in severe ocular surface disease (OSD), which causes blindness, chronic eye irritation and glare. Human amniotic membrane (the innermost lining of the protective sac round a baby in the womb) is commonly used in the surgical treatment of OSD, as it has very similar biological and physical properties to the surface of the eye. It is also possible to grow limbal stem cells from a donated cornea in the laboratory on human amniotic membrane. Human amniotic membrane is routinely collected, at caesarean section birth, from consenting donors and stored at Tissue Banks approved by the Human Tissue Authority. This study is to compare the use of limbal stem cells grown on human amniotic membrane with amniotic membrane on its own as a surgical treatment for OSD.

Who can participate?
You are eligible to take part in the study if you are an adult of either sex and have severe ocular surface disease affecting your sight, which is due to a lack of these special limbal stem cells.

What does the study involve?
A total of 20 patients will take part. Half of the patients will receive treatment with limbal stem cells grown on amniotic membrane and the other half will receive treatment with amniotic membrane alone. Neither you, nor your doctor, will know which treatment you have received, and the treatment will be assigned at random. You will undergo eye surgery to remove the damaged part of your cornea and replace it with either limbal stem cells grown on human amniotic membrane or amniotic membrane on its own. You will have an eye examination and vision test before your surgery and you will be asked to answer some quality of life questions from two standard questionnaires. You will have further eye examinations and vision tests on days 1, 2 or 3, 7 and 14 after surgery and also at 1, 3, 6, 9, 12 15 and 18 months after your surgery, to assess how well the treatment has worked.

What are the possible benefits and risks of taking part?
It is possible that transplanting limbal stem cells grown on amniotic membrane may prove to be

a better treatment for OSD than amniotic membrane alone, but there is no guarantee that this is the case. As with any surgical procedure there is a risk of infection while the wound is healing. You will be given antibiotic and steroid eye drops to promote healing and help prevent infection. There is also the possibility of rejection of the transplanted tissue but you will be prescribed drugs to minimise this risk. All drugs can cause side effects, although many patients never have them. It is possible you may feel sick, suffer from diarrhoea, abdominal pain, tiredness or excess hair growth. These drugs may also lower your resistance to infection.

Where is the study run from?
The study is being run at the Princess Alexandra Eye Pavilion in Edinburgh and the Tennant Institute of Ophthalmology in Glasgow.

When is the study starting and how long is it expected to run?
The study started in February 2012 and patient recruitment will run until 20 patients have been enrolled. Each patient will be followed up on the study for a period of 18 months after surgery.

Who is funding the study?
The study is funded by grants from the UK Stem Cell Foundation, the Chief Scientist Office and Scottish Enterprise.

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2010-024409-11

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
LSC-001

Study information

Scientific Title
Pilot clinical assessment of ex vivo expanded corneal limbal stem cell transplantation in patients with severe ocular surface diseases arising from limbal stem cell deficiency

Study hypothesis
The cornea is the clear front of the eye and its clarity is vital for the transmission of light to the retina for visual perception. The surface of the cornea is made up of a multi-layered epithelium, which is maintained by adult stem cells located in the periphery of the cornea, in a region known as the limbus.

Limbal stem cell deficiency (LSCD) is an irreversible disease resulting from the loss of these corneal epithelial stem cells, or limbal stem cells (LSC), and results in severe ocular surface disease (OSD) characterised by reduced vision or blindness, chronic ocular irritation and visual glare. The corneal epithelium that normally covers the corneal surface becomes deficient and is replaced by the surrounding conjunctival epithelium, resulting in a thickened, irregular, unstable epithelium, often with secondary neovascularisation, inflammatory cell infiltration and disruption of the basement membrane.

Conditions that result in OSD from LSCD have a variety of etiologies and can result in profound morbidity for patients. Aniridia is a primary stem cell disorder, but secondary disorders of the LSC are more common e.g. chemical or thermal burns, Stevens-Johnson syndrome, ocular cicatricial pemphigoid, severe contact lens induced keratopathy or chronic use of toxic topical medications.

The treatment of patients with severe OSD has been largely unsuccessful, with standard corneal transplantation (penetrating or lamellar keratoplasty) providing a stable ocular surface only for as long as the donor epithelium survives. In addition, this procedure carries the risk of rejection of the transplanted tissue, complications and infection. Even with the current approach based on scientific understanding of the role played by limbal stem cells in corneal surface maintenance, patients still face a very poor prognosis resulting in blindness, redness and pain. It is estimated that there are more than 2000 patients in Scotland alone with corneal blindness due to stem cell deficiency.

Several clinical trials have provided evidence to show that grafting viable limbal tissue, either from the fellow healthy eye or a donor eye, with the resident stem cell population may replenish limbal stem cells. However, these techniques have several major limitations. Autologous limbal grafts compromise the healthy donor eyes, while fresh allo-grafts are in short supply and contain Langerhan's and other antigen presenting cells, which increase the risk of graft rejection. Graft materials are stored in organ culture media while the suitability for grafting is evaluated and during this period of storage, limbal stem cells are depleted, rendering the graft material sub-optimal for limbal stem cell transplant. In addition, dissecting a limbal ring transplant from a corneal button is technically demanding and damages the target cell population. Furthermore stem cells are not uniformly distributed around the ring, and it is not always possible to ensure an adequate transfer of stem cells.

Advances in tissue engineering techniques have offered a viable alternative to overcome the limitation of limbal tissue available for transplantation. Much interest has been generated by the prospect of re-implanting ex vivo expanded limbal stem cells as a technique to replenish the corneal surface. Human amniotic membrane (AM) is being extensively used in ocular surface disorders and it has been demonstrated that it can be used as a carrier to expand limbal stem cells in vitro before transfer to the ocular surface (Tsai R. et al. 2000). They achieved visual improvement in 6 cases of OSD secondary to chemical burns and pseudopterygium. Other small observational series report success of this technique to reconstruct the ocular surface (Sangwan VS et al. 2003) and a UK study has recently reported successful ocular surface reconstruction following ex vivo expanded corneal limbal cells (Daya SM et al. 2005). However, a major drawback of this study was the use of murine fibroblast 3T3 feeder layers and foetal calf serum to cultivate limbal stem cells, presenting the risk of transmission of animal borne viruses or acquisition of non-human antigenic substances on the cell membrane during culture.

Ex vivo expanded limbal stem cells on AM are reconstructed from a known quantity of cells and a viable population of stem cells is assured. In autologous transplantation, only a small piece of tissue is required and cells from donors can be tissue typed, expanded and cryopreserved, allowing matching to the recipient's tissue type. In addition, ex vivo expanded cells on AM are devoid of Langerhans cells and other antigen presenting cells, and should, therefore, be less likely to provoke rejection episodes.

This pilot study proposes to investigate the possibility of using donor derived ex vivo expanded limbal stem cells on AM as a technique for replenishing the stem cell population and repairing the corneal surface. Amniotic membrane is already used extensively in ocular surface disorders, although AM alone is not effective in treating total stem cell deficiency. However, it is hypothesised that immunosuppressive therapy and AM may allow ocular surface reconstruction by eliminating the inflammatory environment that is detrimental to the function of stem cells. This is the rationale behind using AM alone as the comparator arm on this study.

A pilot study is necessary because existing knowledge in this therapeutic technique is still limited and, therefore, the data required for reliable sample size calculations is not currently available. In addition, previous studies have used non-human components in their culture techniques, while this pilot study will facilitate evaluation and optimisation of the use of human serum in the ex vivo expansion of corneal limbal stem cells and allow development of a system without non-human substances in the culture media.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North of Scotland Research Ethics Committee, 22/06/2011 (amendment to protocol approved 08 /08/2011), ref: 11/AL/0298

Study design
Randomised controlled single-blind pilot study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Condition
Severe ocular surface disease arising from limbal stem cell deficiency

Interventions
One group of patients will receive donor derived ex vivo expanded corneal limbal stem cells and immunosuppressive therapy, and the second group will receive amniotic membrane graft and immunosuppressive therapy.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
Best corrected visual acuity

Secondary outcome measures
1. Ocular surface score image analysis based evaluation of area of neovascularisation, area of opacity and degree of abnormal fluorescein staining
2. Quality of Life as assessed by validated questionnaires VF14 and SF36
3. Successful re-establishment of corneal surface after treatment, defined as absence of corneal vascularisation, absence of goblet cells on the cornea surface, absence of persistent epithelial defects, smooth corneal epithelium and no staining with fluorescein, non-fibrotic and normal limbal anatomy
4. Engraftment of donor cells

Overall study start date
01/02/2012

Overall study end date
31/12/2013

Eligibility

Participant inclusion criteria
1. Adult patients, of either sex, with corneal blindness due to limbal stem cell deficiency
2. Best corrected visual acuity of 6/18 or less in the worse affected eye. No restriction on best corrected visual acuity in the better eye
3. Severe, debilitating corneal disease with extremely low chance of successful outcome with

limbal and corneal graft surgery
4. Functioning retina indicated by light perception and ultra-sonographic examination to exclude retinal detachment
5. Normal intra-ocular pressure
6. Schirmers test at least 50% normal values

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
20 in total, 10 in each arm

Participant exclusion criteria
1. Inability to give informed, comprehending consent
2. Unfitness for local or general anaesthesia or to give an autologous serum donation
3. Inability to self-administer medication
4. Inability to tolerate immunosuppressive therapy
5. Severe dry eyes
6. Patients with corneal anaesthesia
7. Patients with severe lid deformities
8. Patients with uncontrolled glaucoma or drainage procedures
9. Patients who test positive for any standard donor marker of infection
10. Female patients of a child bearing age who are pregnant, lactating, or not taking adequate contraception

Recruitment start date
01/02/2012

Recruitment end date
31/12/2013

Locations

Countries of recruitment
Scotland

United Kingdom

Study participating centre

NHS Lothian
Edinburgh
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EH3 9HA

Sponsor information

Organisation
NHS Lothian (UK)

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Sponsor type
Hospital/treatment centre

Website
http://www.nhslothian.scot.nhs.uk/

ROR
https://ror.org/03q82t418

Funder(s)

Funder type
Research organisation

Funder Name
UK Stem Cell Foundation (UK) ref: LSC-001

Funder Name
Chief Scientist Office (UK) ref: CZB/4/657

Alternative Name(s)
CSO

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
United Kingdom

Funder Name
Scottish Enterprise (UK) ref: LSC-001

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/05/2017		Yes	No