NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of tissue-cultured limbal stem cell allograft transplantation

The cells that protect the surface of the eye's cornea can be damaged through disease or injury, to the extent that vision is impaired. Limbal stem cell allograft transplantation involves the grafting of stem cells that have been taken from donor eyes and grown in tissue culture, with the aim of improving vision and other symptoms such as eye irritation and dryness.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in September 2006.

Procedure name

- limbal stem cell allograft transplantation

Specialty societies

- Royal College of Ophthalmologists

Description

Indications

Limbal stem cell deficiency (LSCD). The limbus is the part of the eye where the cornea joins the sclera, and where the conjunctiva, covering the sclera, ends. Undifferentiated epithelial cells are produced at the limbus and differentiate to become conjunctival epithelium and also the more specialized corneal epithelial cells. Failure of this process can result in a variety of

serious and intractable disorders of the ocular surface including loss of corneal transparency with reduction in vision. Limbal stem cell production may be damaged by disease processes or following chemical injury.

Current treatment and alternatives

The aim of treatment is to restore a healthy conjunctival and corneal surface. Simple measures include the use of ocular lubricants but surgery is required in more severe cases. Surgical techniques include amniotic membrane grafts which may be combined with limbal stem cell grafts which have not undergone tissue culture, and, where necessary, subsequent corneal grafting.

What the procedure involves

Ex-vivo limbal stem cell allograft transplantation is achieved by harvesting limbal corneal tissue from donor eyes (either matched living relatives or cadaveric donors). The donor stem cells are obtained by excising a small area of the conjunctiva at the limbus and is a minor procedure. The tissue so obtained is then grown in tissue culture and once the cells have multiplied sufficiently, small sheets are transplanted on to the affected eye(s), backed with an amniotic membrane. The surgery is undertaken under either local or general anaesthesia. A protective soft contact lens may be applied, and the eye kept moist with artificial tears in the immediate postoperative period. Systemic immunosuppressants are given in order to minimise the prospect of graft rejection.

Efficacy

Specialist advisers considered the key efficacy outcomes to be graft survival time, and visual acuity.

Most studies report efficacy outcomes relating to LSCD resolution, with parameters including regrowth of the corneal epithelium and resolution of corneal vascularisation. with success rates of between 70% (7/10)[1], and 100% (13/13)[2] of eyes following tissue cultured limbal stem cell transplantation.

In one case series complete restoration of a normal corneal epithelium had occurred in 80% (8/10) eyes by the time the amniotic membrane had dispersed[1]but longer term results are poorer with satisfactory restoration in only 46% (6/13) of eyes at final follow up[3]. In one case series of ten patients there was one (large) persistent and one variable epithelial defect following ex vivo limbal stem cell allograft transplantation[1].

Across the case series identified where this outcome was reported, visual acuity was found to have improved following tissue cultured limbal stem cell transplantation in between 40% (4/10)[1], and 77% (10/13)[2] of eyes, although in some patients concomitant surgery to improve vision was undertaken.

Safety

Donor related transmissible infection, and complications related to immunosupression were thought to be the key safety outcomes relating to this procedure.

The most consistently reported adverse event following tissue cultured limbal stem cell allograft transplantation was bacterial infection. The incidence of this complication ranged from 7% (1/13) eyes[2], through 10 % (1/10) eyes[1], to 15% (2/13) eyes[3].

Glaucoma requiring trabeculotomy was reported in 7% (1/13) of eyes in one case series[3], also the rate of corneal perforation in this series was 31% (4/13) eyes.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to tissue cultured limbal stem cell allograft transplantation. Searches were conducted via the following databases, covering the period from their commencement to 27/07/2006: Medline, PreMedline, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches. (See appendix C for details of search strategy.)

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with partial or total limbal stem cell deficiency.
Intervention/test	Donor cultured limbal stem transplantation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on three case series[2,1,3].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Existing reviews on this procedure

No published reviews were identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in each piece of guidance listed below.

Interventional procedures

- None applicable

Technology appraisals

- None applicable

Clinical guidelines

- None applicable

Public health

- None applicable

Table 2 Summary of key efficacy and safety findings on tissue-cultured limbal stem cell allograft transplantation

Abbreviations used: BCVA, best corrected visual acuity; LSCD, limbal stem cell deficiency; SJS, Stevens–Johnson syndrome			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
Daya S M (2005)[1] **Case series** UK Study period: not stated **n = 10 (10 eyes)** Population: Age = 35 years (range 5 to 62), Male =60%, Congenital disorder n=1, chemical burn n=2, thermal burn n=1, infection n=1, ectodermal dysplasia, n=2, SJS n=3. Indications: Profound limbal stem cell deficiency, inclusion criteria not stated Technique: Limbal tissue obtained from a donor corneoscleral ring, (or harvested from a living donor n=1) grown in culture, and cell sheet on nylon dressing placed onto the ocular surface, covered with an amniotic membrane and sutured to the limbus. Cefuroxime and methylprednisolone applied locally. **Mean follow-up = 28 months** Conflict of Interest. Study funded by trusts, foundations, and associations	**LSCD resolution** The corneal surface of the eye had completely epithelialised by the time the amniotic membrane dispersed in 80% (8/10) of patients. One patient had a large persistent epithelial defect, and one had a variable inferior epithelial defect. Furthermore, success was defined as a marked overall improvement in "negative" components of LSCD (inflammation, conjunctivisation, persistence of corneal epithelial defect, vascularisation, photophobia, and pain) with no single parameter being rated as moderately severe or worse. 70% (7/10) patients were classified as treatment success at final follow up. **Visual acuity** Improvement in visual acuity was achieved in 40% (4/10) of patients. Although 3 of these patients had undergone further procedures.	**Complications** One patient developed bacterial keratitis at 12 months follow up. This resolved but with focal corneal thinning.	Three patients received concomitant procedures at the time of ex-vivo stem cell allograft No details given of case selection method, or accrual procedure. Not stated how many different clinicians undertook the procedure. No independent outcome analysis. No details provided of loss to follow up.

Abbreviations used: BCVA, best corrected visual acuity; LSCD, limbal stem cell deficiency; SJS, Stevens–Johnson syndrome

Study details	Key efficacy findings	Key safety findings	Comments
Shimazaki J (2002)[3] **Case series** Japan Study period: not stated **n = 13 (13 eyes)** Population: Age = 52 years, Male =46%, ocular cicatricial pemphigoid n=3, chemical burn n=2, SJS n=3. Indications: Patients with severe cicatricial keratoconjunctivitis associated with total limb deficiency. Technique: 2x2 mm limbal tissue sample obtained from a cadaveric donor eye n=7, or harvested from a living donor n=6. Grown in culture, on amniotic membrane. Under retrobulbar anaesthetic, the graft was placed on the bare sclera and sutured in place with second amniotic sheet or soft contact lens covering. Eye drops used for intensive epithelial management, and antibiotics given 5 times a day. All but one patients received systemic immunosuppressants . **Mean follow-up = not stated.** Conflict of Interest. Supported by a government grant, no financial interest in products used or mentioned in the study.	**LSCD resolution** At initial follow-up, corneal epithelium regenerated and covered the ocular surface in 62% (8/13) of eyes. At final follow up corneal epithelialisation was achieved in 46% (6/13) eyes, although 3 had partial conjunctival invasion. Recurrence of neovascularisation occurred in 15% (2/13) of eyes.	**Complications** Complication — Rate (eyes) Corneal perforation — 31% (4/13) Infectious keratitis — 15% (2/13) Recurrence of symblepharon — 23% (3/13) Glaucoma, not responding to medical treatment requiring trabeculotomy — 7%(1/13)	Five patients received concomitant keratoplasty Repeat surgery was attempted in one eye with non-epithelialised cornea Not stated how many different clinicians undertook the procedure. No independent outcome evaluation. Final follow up period not stated No details provided of loss to follow up. No criteria given for choice of living related or cadaveric donor graft harvest. Histological evaluation of sample in culture also undertaken, data not extracted here. Time period between onset of limbal cell deficiency and treatment is not stated. The number of limbal stem cells harvested varied between the living donor and cadaveric groups.

Abbreviations used: BCVA, best corrected visual acuity; LSCD, limbal stem cell deficiency; SJS, Stevens–Johnson syndrome

Study details	Key efficacy findings	Key safety findings	Comments
Koizumi N (2001)[2] **Case series** Japan Study period: Jul 1999 to Nov 1999 **n = 11 (13 eyes)** Population: Age = 43 years, Male =60%, ocular cicatricial pemphigoid n=2, chemical burn n=3, SJS (both acute and chronic) n=5, Other =1. Indications: Patients with acute and chronic severe ocular surface disease, clinically diagnosed as total stem cell deficient. Technique: 2x2 mm corneal tissue sample obtained from an eye bank, placed onto denuded amniotic membrane and grown in culture. Conjunctival and subconjunctival tissue removed from eye, and graft secured by sutures, a soft contact lens was used for covering. Ofloxacin, and dexamethasone applied 4 times a day. Corticosteroid and cyclophosphamide given to prevent inflammation and rejection for up to 2 months, and low dose cyclospoirn given for 6 months. **Mean follow-up = 11 months.** Conflict of Interest. Supported by a government grant, authors have no financial interest	**LSCD resolution** At both 2 and 5 days 100% (13/13) of corneas were clear and smooth and the entirely covered with corneal epithelium. Epithelial rejection (sudden onset corneal epithelial damage with inflammation) occurred in 23% (3/13) of eyes at between 2 and 6 months. Corneal surface of eyes with surviving transplants was stable and without defect to final follow up. Conjunctival epithelium invasion onto the corneal surface was reported in 15% (2/13) of patients and also Conjunctival fibrosis in the same proportion **Vision** Improvement in visual acuity (not otherwise defined) was achieved in 100% (13/13) of eyes following surgery. Restoration of good vision (acuity improved by 2 or more lines) was achieved in 77% (10/13) of eyes at 6 months follow up.	**Complications** Complication — Rate (eyes) Difficulty wearing lens due to cicatricial entropion — 7%(1/13) Limited bacterial infection — 7%(1/13)	5 patients underwent concomitant lamellar keratoplasty. Repeat limbal stem cell transplant was undertaken in 1 eye. No details given of case selection, or accrual procedure. Outcomes not independently evaluated. No details provided of loss to follow up. Time period between onset of limbal cell deficiency and treatment is not stated. Authors state that there is no reliable technique to prove cultivated epithelium contains stem cells.

Validity and generalisability of the studies

- Time lag between onset of limbal stem cell deficiency and treatment may influence outcome, this period is not often stated in the study reports.
- Composition and duration of potential immunosuppression regimes are not always adequately described in the studies.
- Great variability of local treatment regimes peri-operatively (from artificial tears to antibiotics and steroids)
- There is considerable variation in aetiology of limbal stem cell deficiency between studies which may influence the efficacy profile of each.
- Not all the studies included in table use culturing to expand limbal stem cells, although all employ amniotic membrane as part of graft.
- The use of living and cadaveric donor tissues varies both between and within some studies.
- Most studies state that limbal stem cell deficiency was total in all patients.

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

Mr D Fraser.

- The specialist adviser considered this procedure to be an established procedure and no longer new.

- The adviser considered that if the graft works well the proceure is highly effective in producing visual benefit.

- Adverse events following the procedure may include graft rejection or failure.

- Additional theoretical complications may include infection by diseased donor tissue, and potential failure of the corneal epithelial stem cell supply in the donor, although this risk was thought to be very small.

- The adviser noted that there are various variations in technique and the most efficacious is yet to emerge, with the need for tissue matching and immunosuppressants requirement still uncertain.

- The adviser did not consider there to be any special training requirement to undertake this procedure.

Issues for consideration by IPAC

- Non English studies excluded as sufficient data in the English language.
- Allograft transplants have been used in many of the included studies where it would appear that only unilateral stem cell deficiency was present. The reason not to use an autograph transplant was not reported in any study.

References

1. Daya SM, Watson A, Sharpe JR et al. (2005) Outcomes and DNA analysis of ex vivo expanded stem cell allograft for ocular surface reconstruction. *Ophthalmology* 112: 470–477.
2. Koizumi N, Inatomi T, Suzuki T et al. (2001) Cultivated corneal epithelial stem cell transplantation in ocular surface disorders. *Ophthalmology* 108: 1569–1574.
3. Shimazaki J, Aiba M, Goto E et al. (2002) Transplantation of human limbal epithelium cultivated on amniotic membrane for the treatment of severe ocular surface disorders. *Ophthalmology* 109: 1285–1290.

Appendix A: Additional papers on tissue-cultured limbal stem cell allograft transplantation not included in summary table 2

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article title	**Number of patients/ follow-up**	**Direction of conclusions**	**Reasons for non-inclusion in table 2**
Fernandes M, Sangwan VS, Rao SK et al. (2004) Limbal stem cell transplantation. *Indian Journal of Ophthalmology* 52: 5–22.	N/A	N/A	Unable to obtain full study report.
Koizumi N, Inatomi T, Suzuki T (2001) et al. Cultivated corneal epithelial stem cell transplantation in ocular surface disorders. *Ophthalmology* ;108: 1569–1574.	n = 2 (3 eyes) FU = 6 months.	The whole ocular surface was covered with transparent epithelium at 5 days follow-up in both patients. The surface was stable without defects at 6 months' follow-up.	Have larger case series in table 2.

Appendix B: Related published NICE guidance for tissue-cultured limbal stem cell allograft transplantation

Guidance programme	Recommendation
Interventional procedures	None applicable.
Technology appraisals	None applicable.
Clinical guidelines	None applicable.
Public health	None applicable.

Appendix C: Literature search for tissue-cultured limbal stem cell allograft transplantation

Database	Version searched	Date searched
Cochrane Library	Issue 2, 2006	27/07/2006
CRD databases (DARE and HTA)	Issue 2, 2006	27/07/2006
Embase	1980 to 2006 Week 29	27/07/2006
Medline	1966 to July Week 3 2006	27/07/2006
PreMedline	1966 to present	27/07/2006
CINAHL	1982 to July Week 4 2006	27/07/2006
British Library Inside Conferences		27/07/2006
NRR	Issue 3, 2006	27/07/2006
Controlled Trials Registry	Issue 2, 2006	27/07/2006

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in other databases.

1 ((limbic or limbal or limbus) adj3 transplant$).tw.

2 exp Limbus Corneae/

3 (cornea adj3 transplant$).tw.

4 ((limbus or limbal or limbic) adj3 cornea$).tw.

5 or/1-4

6 exp Transplantation, Homologous/

7 allograft.tw.

8 Homograft.tw.

9 ((Allograft or homograft) adj3 transplant$).tw.

10 or/6-9

11 exp Eye Injuries/

12 (Eye adj3 (injur$ or trauma or damag$)).tw.

13 Ocular surface disease.tw.

14 exp Ectodermal Dysplasia/

15 Ectodermal dysplasia.tw.

16 Aniridia/

17 Aniridia.tw.

18 Keratoconjunctivitis Sicca/

19 keratoconjunctivitis sicca.tw.

20 Stevens-Johnson Syndrome/

21 Stevens-Johnson syndrome.tw.

22 exp Corneal Diseases/

23 or/11-22

24 5 and 10 and 23

25 animals/

26 humans/

27 25 not (25 and 26)

28 24 not 27

29 from 28 keep 1-102