Prevention of corneal graft rejection

Clinical view

Per Montan, MD, PhD
St Erik Eye Hospital, Stockholm, Sweden
Financial interest?

No!
Optics of the eye

Cornea

Crystalline lens

Retina
Anatomy

1. Limbal conjunctiva
2. Cornea
0.5 mm. Cells express HLA I
Trachoma
Aims of keratoplasty

- Restore a clear visual axis.
- Achieve 20/40 or better VA
  65% do at 2 yrs (Br J Ophthalmol 2002:86: 174 - 80)
Reasons for keratoplasty 1

Endothelial failure – INCREASING!!!

Keratoconus - DECREASING?
Corneal cross-linking - halting keratoconus?
Reasons for keratoplasty 2

- Regrafts - INCREASING
- Scar (following infection, trauma)
Traditional penetrating keratoplasty (PK)
Estimated frequency of keratoplasties, Europe

- EEBA statistics 2008
  4 in 100 000
- Swedish Cornea Registry 2010
  6 in 100 000
- Waiting for an operation in Sweden
  6 in 100 000
- US frequency
  10 in 100 000
Success = a clear graft

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<thead>
<tr>
<th></th>
<th>1 yr</th>
<th>5 yr</th>
<th>10 yr</th>
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<tbody>
<tr>
<td>Kidney¹</td>
<td>91%</td>
<td>89%</td>
<td>79%</td>
</tr>
<tr>
<td>Cornea²</td>
<td>93%</td>
<td>86%</td>
<td>70%</td>
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Notes:
1. Adult first renal transplant 1999-2001
2. First penetrating keratoplasty

(Data from UK Transplant Activity Report, August 2007)
Decay of endothelial cells and rejection

<table>
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<th></th>
<th>1 yr</th>
<th>5 yr</th>
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<tbody>
<tr>
<td>None</td>
<td>90%</td>
<td>81%</td>
<td>71%</td>
</tr>
<tr>
<td>≥1 episode</td>
<td>72%</td>
<td>49%</td>
<td>34%</td>
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(Data from Australian Corneal Graft Registry Report, 2007)
Rejection major threat to transplant survival!!
“Immune privilege” – a misconception

- Keratoplasty induces:
  APC activity (Langerhans and macrophages)
  Clonal expansion of CD4^+ T cells
  Lymph- and hemangiogenesis

15% rejection (usually reversible) at 2 yrs.
Cellular origin in full thickness transplants

- Mixture of donor and recipient cells for > 10 yrs post-op (IOVS. 2009;50:2673-8)
Topical steroids – backbone of $R_x$

- Dexamethasone or prednisolone 7 – 12 months. Lack of RCTs!!!!
- The best regime NOT defined (12 vs. 6 months better, *(Am J Ophthalmol* 2007; 144:318 – 19))
- Value of contd. low-dose $R_x$?
Topical steroids
Risk factors for rejection

- Indication (prev. trauma, infection, iatrogenic endothelial failure, regraft)
- Co-morbidity (glaucoma, infl disease)
- Vascularised recipient bed
- Young age of recipient (pediatric keratoplasty)
- **PREVIOUS REJECTION**
- % of high-risk grafts among operated?
How to deal with high-risk grafting!

- HLA Class I or II matching?
- Systemic immunosuppression?
- Add-on topical $R_x$?
Tissue matching

• Contradictory results.
• HLA Class I matching - beneficial
• HLA Class II matching – even detrimental?
• 3% of EEBA corneal grafts are tissue matched
• 5 year on-going study in the UK – enrolling 1200 pts at risk
Added immunosuppression

- **Oral CsA?**
  *Long-term Rx may be effective*

- **Oral Mycophenolate mofetil?**
  *Equal to CsA*

- **Oral Tacrolimus?**
  *Relatively effective*

- **Lack of protocols combining 2 immunosuppressants!!!**
Added immunosuppression

- **Topical CsA?**
  *At best = steroids.*

- **Topical Tacrolimus?**
  *Potency > steroids?*

- **Both may replace steroids in IOP-responders. Add-on benefit?**
  *No licensed product for ocular use.*
New therapeutic target - neovessels
RCT.
High-risk grafting I

- Observer masking.
- Standard $R_x$ with topical steroids.
- Add-on regimen studied.
- Active Comparator
- Avoid heterogenous populations!
RCT.
High-risk grafting II

- Efficacy endpoints:
  Rejection episodes within 2 - 3 yrs
  Clear graft
  Vascular activity
  Visual Acuity
  Pachymetry and ECD may be of value
  VF questionnaire

- Safety variables:
  Ocular (surface, IOP)
  Systemic (hematology, liver, kidney)
"Corneal clarity"...

Scheimpflug imagery (JCRS 2010;36: 2105-2114)
Slit lamp digital photos of neovessels
Other ways to avoid rejections

- Lamellar grafting
- Keratoprosthesis
- Biosynthetic cornea
Anterior lamellar keratoplasty

- DALK replaces anterior cornea only
- No endothelial rejection!!!!!!
- Indications: Keratoconus, stromal dystrophies, non-penetrating scars
Posterior lamellar keratoplasty

- DSAEK, DMEK replaces endothelium
- Endothelial rejection.
  Frequency < penetrating method?
  Severity < penetrating method!
Limbal stem cell deficiency (LSCD)

- Very rare conditions (Stevens-Johnson, OCP, aniridia)
- Ocular burn
Dry eye – a contraindication to any restoration project

• Abort!
Unilateral disease. Autologous stem cell transplantation
Autologous explants
Post-op course with recurrence...
Allogeneic limbal stem cell transplantation
Post-op improvement
Ex vivo expansion of limbal stem cells

- Migration or separation of LSCs from a small limbal biopsy on a carrier.
- Animal products usually involved
- Transfer to recipient eye easier AND limited use of autologous eye tissue.
- Cultivation in licensed cell laboratories!
Success of LCS grafting = a stable and avascular surface

- Autologous grafts: 75 – 100% (free explants = cultivated cells)
- Allogeneic grafts: 30 – 75%
- Remaining poor vision may be restored with keratoplasty
(R?)CT.

Stem cell restoration a

• Observer masking.
  Explant vs. culture?
  Culture vs. culture?
  Different immunosuppressive protocols for allogeneic transplants?
(R?)CT.
Stem cell restoration b

- Efficacy endpoints at 1 - 2 yrs:
  Corneal epithelial parameters
  (vital staining, superficial transparency, regress of vessels).
  Impression cytology?
  VA
  Pain, Photophobia
  VF questionnaire
- Safety (vide supra)
Unmet needs.

Summary

• Best topical steroid regime for low-risk grafts.

• Add-on value of topical immuno-suppressants and/or anti-angiogenic Rx

• Systemic immunosuppression/HLA-matching in high-risk grafting and allogeneic stem cell transplants.

• Development of gold standard cultivation of LSCs