Long-term Outcomes of Keratolimbal Allograft for Total Limbal Stem Cell Deficiency Using Combined Immunosuppressive Agents and Correction of Ocular Surface Deficits

Lingyi Liang, MD, PhD; Hosam Sheha, MD, PhD; Scheffer C. G. Tseng, MD, PhD

Objective: To determine the long-term outcomes of keratolimbal allograft (KLAL).

Methods: Scores of such risks as infrequent blinking, blink-related microtrauma, conjunctival inflammation, elevated intraocular pressure, dry eye, symblepharon, lagophthalmos, and previous KLAL or penetrating keratoplasty (PKP) failure were calculated and recorded before, during, and after KLAL. Prolonged oral mycophenolate mofetil and tacrolimus and short-term prednisone and acyclovir were administered in 12 eyes (10 consecutive patients) with total limbal stem cell deficiency after KLAL. Ten eyes underwent subsequent PKP.

Results: More corrective measures were required in eyes with higher risk scores. During a follow-up of 61.2 months (standard deviation [SD], 18.2; range, 36-91 months) after KLAL, postoperative epithelial breakdown due to exposure occurred late in the period after PKP and remained a primary risk. Mean daily doses of 1.4 g of mycophenolate mofetil and 1.6 mg of tacrolimus were administered for 52.7 months (SD, 22.5; range, 23-91 months) with few adverse effects and reached trough levels of 1.6 µg/mL (SD, 0.6 µg/mL) and 4.5 ng/mL (SD, 2 ng/mL), respectively. Keratolimbal allograft and PKP rejection was noted in 2 and 3 eyes, respectively, though there was a reversal in 1 eye in each group, yielding final KLAL and PKP survivals in 10 and 8 eyes, respectively, and ambulatory visual acuity of up to 20/20 in 10 eyes for 67.2% of the entire follow-up period.

Conclusion: Correction of ocular surface deficits combined with an immunosuppressive regimen further improves the long-term outcome of KLAL in eyes with total limbal stem cell deficiency.


The maintenance of a healthy corneal epithelium relies on stem cells located at the limbus. When limbal stem cells or their supportingstromal environment is destroyed, corneal blindness occurs. Histologically, corneas with limbal stem cell deficiency (LSCD) carry the hallmark of conjunctivalization associated with chronic inflammation, superficial neovascularization, scarring, and poor epithelial integrity. Consequently, patients with LSCD experience severe photophobia and decreased vision.

Conventional penetrating keratoplasty (PKP) is contraindicated. Visual rehabilitation for LSCD resorts to transplantation of autologous or allogeneic limbal stem cells, depending on the laterality, the extent of involvement, and the patient’s compliance. For bilateral total LSCD, or in unilateral total LSCD when the fellow eye is not chosen as a donor, transplantation of allogeneic limbal stem cells is achieved by either limbal conjunctival allograft from living, related donors or keratolimbal allograft (KLAL) from cadaveric donors or both. Compared with limbal conjunctival allograft from living, related donors, KLAL provides more stem cells without compromising the healthy limbal tissue in a normal eye.

Transplantation of an allograft poses a high risk of rejection even in HLA-matched recipients. Therefore, KLAL survival depends on systemic immunosuppression for a prolonged, if not indefinite, period. Immunosuppression using topical and systemic steroids and cyclosporine A cannot halt allograft rejection in high-risk PKP or KLAL. Combined systemic immunosuppression based on mycophenolate mofetil and tacrolimus has been shown to be more effective and safer than cyclosporine A in promoting the survival in solid organ transplantations by lessening acute rejection and can reduce rejection in high-risk PKP. However, it remains unclear whether this regimen is also effective...
in prolonging the survival of KLAL and, if so, what the optimal long-term dosages is.

Although KLAL rejection is considered the major cause of failure, it only accounts for a part of reported cases. In fact, such risk factors as keratinization, symblepharon, inflammation, and dry eye have been implicated for KLAL failure. We wonder whether there are as-yet-unknown clinical variables that might affect the KLAL outcome and whether measures taken to correct these risk factors may augment aforementioned immunosuppression to improve the KLAL outcome.

### METHODS

#### PATIENTS

This study was approved by the Baptist Health South Florida institutional review board (Miami, Florida) to retrospectively review the medical records of 10 patients (12 eyes) with LSCD who were consecutively operated on by 1 surgeon (S.C.G.T.) at the Ocular Surface Center, Miami, from 2001 through 2005. All patients completed at least 36 months of follow-up after KLAL. Their clinical data concerning preoperative diagnosis, previous operations, measures taken to correct ocular surface deficits, outcomes, and complications were retrieved. Diagnosis of LSCD was confirmed in 2 eyes by impression cytology that showed goblet cell on the corneal surface and in 10 eyes by late fluorescein staining, loss of limbal palisade of Vogt, and superficial vascularization.

#### OCULAR SURFACE DEFICIT SCORES

To gauge the overall risk that may lead to graft failure or rejection, we arbitrarily assigned a total score by assigning 1 point for each of the following 7 ocular surface deficits: infrequent blinking; blink-related microtrauma due to eyelid margin abnormalities, such as malposition, scar, keratinization, or misdirected lashes as previously defined; conjunctivitis; increased intraocular pressure (IOP); aqueous tear–deficient dry eye; lagophthalmos; and pathogenic symblepharon as recently defined; as well as 1 point each for prior KLAL or PKP failure (Table 1).

<table>
<thead>
<tr>
<th>Case No./Sex</th>
<th>Age</th>
<th>Eye</th>
<th>Cause of LSCD</th>
<th>Previous Operations</th>
<th>Infrequent Blinking</th>
<th>Conjunctivitis</th>
<th>Increased IOP</th>
<th>Dry Eye</th>
<th>Lagophthalmos</th>
<th>Pathogenic Symblepharon</th>
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<td>CB, PKP</td>
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<td>CB</td>
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</table>

Abbreviations: AMT, amniotic membrane transplantation; BRMT, blink-related microtrauma, CB, chemical burn; CE, cataract extraction; FR, fornix reconstruction; IOL, intraocular lens implantation; IOP, intraocular pressure; KLAL, keratolimbal allograft; LKP, lamellar keratoplasty; LSCD, limbal stem cell deficiency; PKP, penetrating keratoplasty; SJS, Stevens-Johnson syndrome; T, tarsorrhaphy.

#### SURGICAL TECHNIQUES OF KLAL AND AMNIOTIC MEMBRANE TRANSPLANTATION

All operations were performed under general anesthesia and included KLAL and amniotic membrane transplantation, similar to what has previously been reported with some modifications. Briefly, pannus and scar tissue were removed from the limbal and corneal surfaces. The denuded corneal and limbal and some of the bulbar surface was covered by a sheet of cryopreserved amniotic membrane (Bio-Tissue, Miami) with sutures in 10 eyes and with fibrin glue (Baxter Inc, AG, Vienna, Austria) in 2 eyes. Following a 7.5- to 8.0-mm trephination, the remaining donor ring without HLA matching was prepared for KLAL by trimming off the excess sclera, removing the posterior half of the stroma, and tapering both corneal and scleral edges. After KLAL was secured to the recipient’s conjunctival edge with interrupted 10-0 nylon sutures, another layer of amniotic membrane was sutured by a purse-string running 10-0 nylon sutures in 11 eyes, or ProKera (Bio-Tissue) was inserted in 1 eye. Temporary sutured tarsorrhaphy was performed in 11 eyes and permanent tarsorrhaphy in 1 eye.

#### IMMUNOSUPPRESSIVE REGIMENS

All patients received both 1 g of oral mycophenolate mofetil and 1 mg of tacrolimus twice a day starting 1 week preoperatively and 0.5-mg/kg prednisone daily and 200 mg of acyclovir 5 times daily starting 3 days prior to surgery. Both prednisone and acyclovir were tapered off 2 to 3 months postoperatively when the ocular surface was not inflamed. The trough levels of mycophenolate mofetil and tacrolimus were checked every 1 to 3 months, and their doses were adjusted according to ocular surface inflammation and systemic adverse effects that mycophenolate mofetil and tacrolimus are known for based on blood pressure and levels of creatinine, blood urea nitrogen, complete blood count, platelets, and liver profile evaluated at baseline and every 1 to 3 months. When the ocular surface was not inflamed, dosages of mycophenolate mofetil and tacrolimus were tapered to 0.3 g and 0.25 mg/kg per day, respectively, and discontinued if irreversible graft failure or significant adverse effects were noted.
OTHER POSTOPERATIVE MANAGEMENT

Postoperatively, topical ofloxacin (Allergan, Irvine, California) and prednisolone acetate, 1% (Allergan), or unpreserved dexamethasone, 0.1%, eye drops were applied 4 times a day. Treatment with ofloxacin was discontinued when epithelialization was completed but resumed if there was a corneal epithelial defect. Dexamethasone dosage was tapered off in 2 to 3 months after the ocular surface became uninfluenced. The suture for temporary tarsorrhaphy was removed usually 2 weeks after surgery or when the amniotic membrane dissolved, and a bandage contact lens, such as Night and Day (CIBA Vision, Duluth, Georgia) and a scleral lens from Kontur Kontakt Lens Co (Hercules, California) were inserted. During follow-up, increased limbal inflammation or vascular engorge-ment with or without corneal epithelial defects1 was treated with subconjunctival injection of 20 mg of triamcinolone (Bristol-Myers Squibb, Princeton, New Jersey) and hourly topical steroid drops and an increase in mycophenolate mofetil and tacrolimus dosages to the preoperative level. Any epithelial breakdown, such as irregular epithelium, superficial punctate keratopathy, or epithelial defect, was promptly treated according to the underlying cause. Infrequent blinking and/or increased scleral show was managed by encouraging blinking and by punctal occlusion with or without autologous serum 4 times a day, followed by permanent tarsorrhaphy. A bandage contact lens was used continuously and an autologous serum was used until an intact epithelium remained stable. For eyes with total punctal occlusion and extended wear of bandage contact lens, irrigation of preservative-free saline solution twice daily was instructed. Recurrent trichiasis was corrected by periodic epilation. Eyelid malposition or deformity, resulting in blink-related microtrauma and/or lagophthalmos, was corrected by eyelid reconstruction. Pathogenic symblepharon was treated by symblepharon lysis, fornix reconstruction, and amniotic membrane transplantation as recently reported.28

OUTCOME MEASURES

The first outcome measure was the change in best-corrected visual acuity from before to after surgery and in the postoperative period during which ambulatory vision (defined as a best-corrected visual acuity ≥20/200) was maintained similar to visual acuities reported by Dohman and Terada26 in patients with keratopros-thesis. The second outcome measure was KLAL survival, evidenced by the maintenance of an intact and stable corneal epithelium post-operatively. In contrast, KLAL failure was indicated by recurrent late fluorescein staining, conjunctivalization of the cornea, or persistent epithelial breakdown after the aforementioned corrective measures.17 The third outcome measure was conventionally defined PKP survival, while PKP failure was diagnosed by classical signs of endothelial or epithelial rejection lines and subepithelial infiltrates, keratic precipitates, stromal edema, and corneal opacity.

RESULTS

These 10 patients included 8 males and 2 females with a mean age of 50.2 years (standard deviation [SD], 15 years). Limbal stem cell deficiency was bilateral in 8 and unilateral in 2 patients (cases 9 and 10) and caused by chemical burns (10 eyes [83%]) and Stevens-Johnson syndrome (case 3); case 1 was idiopathic. Table 1 lists cases eyes ranked by preoperative risk score. The more severe cases (cases 6 to 10) had received more prior operations. Except for case 1, all had infrequent blinking. Blink-related microtrauma, conjunctival inflammation, increased IOP, and aqueous tear–deficient dry eye were found in more than 50% of eyes. Lagophthalmos or pathogenic symblepharon was found in cases 7 to 10, and prior PKP or KLAL failure was found in cases 6 to 10. Preoperatively, measures were taken to correct all ocular surface defects, except for infrequent blinking (Table 2). A nonpreservative steroid was applied in 7 eyes with conjunctival inflammation. Intraocular pressure was controlled medically in 4 eyes and by implantation of a glaucoma drainage device in another 3 eyes. Punctal occlusion, artificial tears, and/or autologous serum was applied in all 6 eyes with dry eye. Eyelid reconstruction was performed in 2 eyes with blink-related microtrauma caused by eyelid malposition. Fornix reconstruction and amniotic membrane transplantation were performed in 2 eyes with pathogenic symblepharon as recently reported.28 Bandage contact lenses were inserted in 2 eyes with large epithelial defects. Epilation was also performed in those with misdirected lashes.

Keratolimbal allograft/amniotic membrane transplantation was uneventfully performed in all 12 eyes. Intrapro-"
without postoperative epithelial breakdown had a low risk score of less than 5; among them 2 did not undergo PKP.

Systemic immunosuppression was continued in all 8 patients in whom it was successful without any known significant adverse effects, though it was discontinued in 2 patients in whom it had failed because of irreversible PKP rejection (case 9) and persistent hypertension (case 10). As a result, it had been used for 52.7 months (SD, 22.5 months) in all patients, ie, 86% of the entire follow-up period. Per-Permanent rejections were noted in 2 eyes of cases 9 and 10. Keratolimbal allograft graft melt at the 12- to 3-o’clock position limbus was noted in 1 eye (case 10) with severe dry eye, and exposure because of lagophthalmos and exotropia. Among the other complications, there was no postoperative infection.

### Table 2. Corrective Measures, Operations, Complications, and Final Outcome

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Corrective Measures</th>
<th>PKP, mo Post-KLP</th>
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<th>Outcome Measures</th>
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<td>Postoperative, Early/Late</td>
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<td>2 BCL/#T</td>
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</table>

### Abbreviations
- AG: anti-glaucoma medications
- AS: autologous serum
- BCL: bandage contact lens or scleral lens
- CF: counting fingers
- C: chemical burn
- ED: epithelial defect
- F: failure
- GDD: glaucoma drainage device implantation
- H: hand motion
- IOP: intraocular pressure
- IR: irreversible
- KP: keratolimbal allograft
- LR: eyelid reconstruction
- MMC: mitomycin C
- NA: not applicable
- PO: punctual occlusion
- PKP: penetration keratoplasty
- P: penetration
- R: reversible
- S: successful
- SPK: superficial punctuate keratopathy
- V: visual acuity
- #T: permanent tarsorrhaphy
- #T: temporary tarsorrhaphy

### Table 2 Notes
- a Measures taken immediately after KLAL (early) and later when corneal epithelial breakdown ensued (late).
- b Starting when ED occurs but not immediately after KLAL.
For visual rehabilitation, cataract extraction and intraocular lens implantation were performed in 1 eye after KLAL (case 3) and in 6 eyes during PKP. Best-corrected visual acuity improved from hand movement to 20/200 (before KLAL) to ambulatory 20/200 to 20/20 in 10 eyes (cases 1 to 8) at the last visit. Furthermore, the ambulatory vision was maintained for 41 months (SD, 26.9; range, 3-90 months), accounting for 67.2% of the entire post-KLAL follow-up period. Ten of 12 eyes (83%) maintained uninflamed ocular surfaces, which is no different from eyes receiving conjunctival limbal autograft (Figure 3). The second outcome measure showed that these eyes also maintained KLAL survival (Figure 3). The third outcome measure showed that 8 of 10 eyes (80%) maintained PKP survival, resulting in a stable and smooth corneal epithelium (Figure 3). The failure in cases 9 and 10, with the highest risk scores, was associated with irreversible KLAL and penetrating keratoplasty graft failure 3 months later (F).

**COMMENT**

Although KLAL with or without PKP has been advised for restoring vision in eyes with total LSCD, its outcome is not simply determined by successful transplantation of limbal stem cells, but can also be adversely affected by several risk factors threatening ocular surface health. We know that ocular surface health depends on a stable preocular tear film that helps supply oxygen to an avascular clear cornea when the eye is open. To achieve this goal, ocular surface epithelia, all external adnexal glands, and eyelids work in concert via neuroanatomic integration by 2 neural reflexes controlling secretion of different tear components and eyelid blinking/closure. The present study illustrates what ocular surface deficits are prevalent and threatening and how corrective measures may augment the long-term success of KLAL for eyes with total LSCD.

Among ocular surface deficits, we have identified infrequent blinking, blink-related microtrauma, conjunctival inflammation, increased IOP, aqueous tear-deficient dry eye, lagophthalmos, pathogenic symblepharon, and prior KLAL or PKP failure as potential risk factors. As summarized in Tables 1 and 2, 11 of 12 eyes initially had 1 or more risk factors before KLAL. Eyes with higher scores had more prior failed operations, required more corrective measures, developed more postoperative corneal epithelial breakdown, showed more KLAL/PKP rejections, resulted in irreversible rejection, and had overall poor outcomes. Keratinization, symblepharon, inflammation, and dry eye have been
recognized as potential risk factors in eyes receiving KLAL. In this study, only case 3 had mild eyelid margin keratinization, which caused blink-related microtrauma. Glaucoma is a known risk factor for PKP. Schwartz et al proposed a prognostic staging system according to underlying diseases with or without inflammation. Besides these, we also identified 3 other risk factors, namely, infrequent blinking, blink-related microtrauma, and lagophthalmos; the former 2 were present in the overwhelming majority of our cases, while the last 1 was presented in 3 severe cases (Table 1).

Together, these 3 factors could destabilize the precorneal tear film, hence contributing to postoperative epithelial breakdown and PKP failure as illustrated in case 8 (Figure 1G and H). Blink-related microtrauma could further damage the ocular surface epithelium and cause inflammation. Future studies are needed to determine whether a risk score as proposed herein can help predict the outcome in studies with a larger sample size.

Identification of these risk factors helped us formulate a corrective strategy before, during, and after KLAL. Nine of 12 eyes required at least 6 types of corrective measures (Table 2). Similar to what has been reported, punctal occlusion, artificial tears, autologous serum, bandage contact lenses, and tarsorrhaphy were needed in all patients (except for case 1) (Table 2). Previously, epithelial defect was considered 1 major postoperative complication in 36% to 73% of eyes receiving KLAL with or without PKP, while 37% to 83% of these defects lead to PKP failure. We believed that such postoperative complications should also include superficial punctate keratopathy and any irregular epithelium, as they might precede an epithelial defect (cases 2, 5, 6, and 8). Previous studies, however, did not provide information linking epithelial breakdown to PKP.

Herein, we noted that such epithelial breakdown still developed late after PKP in 9 of 12 eyes despite all aforementioned measures. A continuous follow-up to protect against any insult to the ocular surface cannot be overstated. Such conventional measures as punctal occlusion, artificial tears, and autologous serum drops were not sufficient. Extended bandage contact lens wear not only protected the eye from blink-related microtrauma during blinking, but also held a stable precorneal tear film in eyes with infrequent blink. We did not note any bandage contact lens–associated infectious keratitis during the entire follow-up, when eyes also received topical antibiotic eye drops only during epithelialization and daily irrigation with preservative-free saline. The remaining exposure problem due to increased scleral show was solved by permanent tarsorrhaphy, while problems due to lagophthalmos were solved by other reconstructive operations. As a result, 7 of 9 eyes with epithelial breakdown healed and maintained a stable corneal epithelium and helped improve the surgical outcome.

Combined immunosuppressive agents also play a role in our long-term maintenance of a clear and functional graft. Before KLAL, patients had their routine check-ups with an internist to rule out underlying diseases, such as significant hypertension, liver or kidney dysfunction, and hematocytopenia, all of which may affect the use and dosage of systemic immunosuppressants. During immunosuppressant treatment, internists and transplant specialists were consulted if there was any issue related to toxicity. The goal of immunosuppression is to keep the eye uninflamed, which the ophthalmologist monitors to avoid systemic adverse effects, which are monitored by an internist. Our daily dosages were less than 2 g of mycophenolate mofetil and 2 to 12 mg of tacrolimus, which are routinely used in liver or renal transplantation, and reached an average trough level that was also less than the target level of 8 to 13 ng/mL for tacrolimus. This might explain partly why there were fewer and milder adverse effects in these patients than in those receiving liver or renal transplantation. Alloway et al also noted that combined mycophenolate mofetil and tacrolimus resulted in significantly fewer systemic adverse effects in KLAL patients than renal transplant patients. The PKP rejection rate was 30%, not significantly different from 46% (28 eyes), 15% (7 eyes), and 64% (14 eyes) (all P > .05) when systemic cyclosporine A was used alone. However, the KLAL rejection rate was 17%, which is significantly lower than the 80% rate in 5 eyes receiving a daily dose of 4.4 mg of tacrolimus alone and 87.5% in 15 eyes receiving cyclosporine A alone (both P < .01). Because 5 of 7 rejections occurred shortly after trichiasis, loose sutures,
dry eye, or remaining exposure, we believe that the primary cause of rejection was recurring or persistent ocular surface deficits. Indeed, 4 such episodes were reversed after adjusting immunosuppressant doses and correcting the remaining ocular surface deficits. It is likely that previous failed KLALs in eyes with the highest risk scores decreased the success rate of subsequent KLALs despite adnexal surgery, corrective measures, and strong immunosuppression. Future studies are needed to address this likelihood and to determine whether these eyes require a different immunosuppressive regimen.

Judged by all 3 outcome measures, aforementioned corrective measures and combined immunosuppressive treatment resulted in a long-term (more than 3 years) success rate of 80% to 83%, significantly higher than the long-term (over 2 years) success rate of less than 50% reported by others (a total of 121 eyes) (P < .05) with various ocular surface diseases13,15-17,23 but comparable with the long-term (an average of 3 years) success rate of 74.2% in 31 eyes (with aniridia11 when oral cyclosporin A alone is administered (over 2 years) success rate of less than 50% reported by others). A total of 121 eyes with preoperative KLAL in 2000 in eyes with total LSCD caused by different diseases.

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Correspondence: Scheffer C. G. Tseng, MD, PhD, Ocular Surface Center, 7000 SW 97 Ave, Ste 213, Miami, FL 33173 (stsgeng@ocularsurface.com).

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