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Ophthalmic Technology Assessment

Outcomes and Complications of Limbal Stem Cell Allograft Transplantation

A Report by the American Academy of Ophthalmology

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Purpose: To review the published literature on the safety and outcomes of keratolimbal allograft (KLAL) transplantation and living-related conjunctival limbal allograft (lr-CLAL) transplantation for bilateral severe/total limbal stem cell deficiency (LSCD).

Methods: Literature searches were last conducted in the PubMed database in February 2023 and were limited to the English language. They yielded 523 citations; 76 were reviewed in full text, and 21 met the inclusion criteria. Two studies were rated level II, and the remaining 19 studies were rated level III. There were no level I studies.

Results: After KLAL surgery, best-corrected visual acuity (BCVA) improved in 42% to 92% of eyes at final follow-up (range, 12–95 months). The BCVA was unchanged in 17% to 39% of eyes and decreased in 8% to 29% of eyes. Two of 14 studies that evaluated the results of KLAL reported a notable decline in visual acuity over time postoperatively. Survival of KLAL was variable, ranging from 21% to 90% at last follow-up (range, 12–95 months) and decreased over time. For patients undergoing lr-CLAL surgery, BCVA improved in 31% to 100% of eyes at final follow-up (range, 16–49 months). Of the 9 studies evaluating lr-CLAL, 4 reported BCVA unchanged in 30% to 39% of patients, and 3 reported a decline in BCVA in 8% to 10% of patients. The survival rate of lr-CLAL ranged from 50% to 100% at final follow-up (range, 16–49 months). The most common complications were postoperative elevation of intraocular pressure, persistent epithelial defects, and acute allograft immune rejections.

Conclusions: Given limited options for patients with bilateral LSCD, both KLAL and lr-CLAL are viable choices that may provide improvement of vision and ocular surface findings. The studies trend toward a lower rejection rate and graft failure with lr-CLAL. However, the level and duration of immunosuppression vary widely between the studies and may impact allograft rejections and long-term graft survival. Complications related to immunosuppression are minimal. Repeat surgery may be needed to maintain a viable ocular surface. Reasonable long-term success can be achieved with both KLAL and lr-CLAL with appropriate systemic immunosuppression.

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The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review the available research for clinical efficacy, effectiveness, and safety. After review by members of the Ophthalmic Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment by the Ophthalmic Technology Assessment Committee Cornea and Anterior Segment Disorders Panel was to review the published literature on the safety and outcomes of keratolimbal allograft (KLAL) transplantation and living-related conjunctival limbal allograft (lr-CLAL) transplantation for the treatment of limbal stem cell deficiency (LSCD).

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Background

The corneal epithelium plays a critical role in the health of the ocular surface, corneal integrity, and ultimately vision. This epithelial layer is continually renewed and replaced. The source of the stem cells responsible for this constant regenerative process is located at the limbus[1,2] within the palisades of Vogt.[3] The limbal stem cells also provide a functional barrier between the corneal and conjunctival epithelium.

The loss of limbal stem cells can lead to significant ocular morbidity.[4] Symptoms of LSCD include photophobia, pain, redness, and decreased vision. On clinical examination, findings may range from a stippling fluorescein staining in a whorled-like pattern of epithelium on the cornea to persistent nonhealing epithelial defects, with or without neovascularization and scarring of the cornea. In 2012, a Limbal Stem Cell Working Group was established to create a global consensus statement on LSCD, including disease staging as determined by the extent of limbal involvement and how the central 5 mm of the corneal epithelium is affected.[4]

Limbal stem cell deficiency is associated with different conditions, including primary genetic disorders such as aniridia and epidermal dysplasia, or secondary causes of LSCD, including chemical and thermal injuries, Stevens-Johnson syndrome/toxic epidermal necrolysis, mucous membrane pemphigoid, multiple ocular surgeries, use of antimetabolites, prior radiation, and contact lens overwear.

The treatment options for patients with LSCD depends largely on the extent of limbal involvement (partial vs. total LSCD), the extent of conjunctival deficiency, and whether the disease is unilateral or bilateral.[5] For patients with mild partial LSCD, supportive treatment with lubrication, autologous serum tears, plasma-rich growth factors eye drops, and scleral lenses may be an appropriate option to help alleviate symptoms and improve visual acuity.[6] Lateral tarsorrhaphy may help in cases of partial LSCD. Amniotic membrane transplantation and plasma-rich growth factors fibrin membranes also have been used with or without superficial keratectomy to treat cases of partial LSCD.[7–11]

In the case of total LSCD, limbal stem cell transplantation (LSCT) options must be considered. Patients with unilateral total LSCD may benefit from autologous LSCT via simple limbal epithelial transplantation (SLET),[12] conjunctival limbal autograft,[13] and cultivated limbal epithelial transplantation with generally good long-term success.[14–18]

In contrast, bilateral total LSCD remains a devastating condition for which treatment options remain limited. The predominant treatment options include KLAL from cadaveric donors, lr-CLAL from living-related donors, conjunctival limbal allograft procedures, or keratoprosthesis surgery. Newer techniques include allogenic SLET.[19] All these options have associated risks and benefits, and long-term outcomes continue to be guarded for these patients.

Question for Assessment

The focus of this assessment is to address the following question: What are the outcomes and complications of limbal conjunctival allograft transplantation from living-related donors (lr-CLAL) or KLAL transplants from cadaveric donors for patients with total LSCD?

Description of Evidence

Literature searches of studies in the English-language were last conducted in the PubMed database in February 2023 without date restrictions. Key words in the search were the following MeSH headings: ((((((*limbal stem cell deficiency* OR *limbal stem cell deficiency disease lscd* OR *limbal stem cell deficiency lscd*))) OR LSCD))) (*limbus OR limbal* OR *limbus cornea*[MeSH Terms]) (*transplant* OR *transplantation autologous* OR *stem cell transplantation*[mh] OR transplant* ((*conjunctival limbal autograft* OR *conjunctival limbal autograft clau* OR CLAU OR *cultivated limbal stem cell transplantation*[tw] OR CLET OR *keratolimbal allografts* OR *keratolimbal allografts klal* OR KLAL OR *limbal stem cell transplantation* OR *limbal stem cell transplantation lsct* OR LSCT OR *living related conjunctival allograft lr clal* OR *living related conjunctival limbal* OR *living related conjunctival limbal allograft* OR LR-CLAL OR *simple limbal epithelial transplantation* OR *simple limbal epithelial transplantation slet* OR SLET))) keratolimbal allograft* (((limbal[tw] OR keratolimbal[tw])) AND (stemcell*[tw] OR stem cell*[tw] OR allograft*[tw] OR transplant*[tw])) ((chemical[tw] OR thermal[tw])) AND (injuries[tw] OR injury[tw] OR burn*[tw]) ((stevens-johnson syndrome[mh] OR (*stevens johnsons syndrome* OR *stevens johnson syndrom**) OR stevens johnson syndrome[tiab])) aniridia[tw] ((((autograft*) OR cultivated graft*) OR cultured graft*)).

The search yielded 523 articles. After reviewing the abstracts, 76 that addressed lr-CLAL or KLAL were selected and reviewed in full text for relevance. Of these articles, 21 met the inclusion criteria based on the study design and the number of eyes reported in the study. Studies were limited to those that included at least 10 eyes with a minimum mean follow-up of 12 months. The reviewers were not masked to the names of the publications or the authors. When multiple articles were written by the same group of authors during a similar time frame, only the article with the largest series of eyes was included to prevent undue bias from any single center. Visual acuities were converted from logarithm of the minimum angle of resolution and decimal values as needed to the Snellen equivalent to allow for comparison between studies.

The panel methodologist (R.M.S.) assigned a level of evidence rating to each of the 21 selected articles based on the rating scale developed by the Oxford Centre for

Table 1. Summary of Studies On and Outcomes of Keratolimbal Allograft Transplantation

Author(s) and Year	Level of Evidence	No. of Eyes	Etiology of LSCD	Mean (Range) Follow-up in Months	Preoperative BCVA	Postoperative BCVA	Survival (%)	Concurrent Corneal Procedures*	% Use of AMT	Postoperative Systemic Immunosuppression	Postoperative Topical Steroid/ Anti-inflammatory
Solomon et al, 2002[21]	III	39	CB, SJS, OCP, atopic keratoconjunctivitis, aniridia, other secondary stem cell deficiency	34.0 (12–117.6)	100% < 20/200	% ≥ 20/200: 76.6% @ 1 yr 53.6% @ 3 yrs 44.6% @ 5 yrs	76.9% @ 1 yr 66.5% @ 2 yrs 47.4% @ 3 yrs 23.7% @ 5 yrs	61.5% PKP	100	CsA	Methylprednisolone 1%
Ilari and Daya, 2002[23]	III	23	SJS, CB, OCP	60 (15–96)	20/100 to LP	Range: 20/50 to LP VA improved: 43.5% VA unchanged: 39.1% VA decreased: 17.4%	54.4% @ 1 yr 33.3% @ 2 yrs 27.3% @ 3 yrs 21.2% @ last follow-up	60.9% PKP 13.0% LK	21.7%	Methylprednisolone Prednisolone CsA	Dexamethasone 0.1% CsA
Maruyama-Hosoi et al, 2006[24]	III	85	SJS, OCP, pseudo-OCP, CB, other secondary stem cell deficiency	46.6 (NR)	NR	NR	65.9%	65.9% PKP 18.8% LK	100%	CsA Dexamethasone	Dexamethasone 0.1% CsA 0.05%
Wylegala et al, 2008[22]	III	43	CB, OCP, SJS, postinflammatory	31.2† (6–72)	20/200 –20/2000	VA improved: 53.5% @ 6 mos 34.9% @ 12 mos	59.4% @ 3 yrs (includes 26 lr-CLAU) 46.4% @ 6 yrs (includes 26 lr-CLAU)	NR	NR	NR	NR
Liang et al, 2009[28]	III	12	CB, SJS, idiopathic	61.2 (36–91)	20/200 to LP	20/20–20/200: 83% <20/200: 17% VA improved: 92% VA decreased: 8%	83%	41.6% intraoperative MMC	100%	MMF Tacrolimus Prednisone	Prednisolone acetate 1% or dexamethasone 0.1%
Hong et al, 2011[25]	III	23	CB	12 (12)	20/50 to LP	Range: 20/30 to LP VA improved: 65.2% VA unchanged: 17.4% VA decreased: 17.4%	90.0% @ 6 mos 60.9% @ 12 mos	17.4% PKP 8.7% LK	NR	Dexamethasone CsA	Dexamethasone 0.1% CsA 0.05%
Javadi et al, 2011[36]	III	40	Mustard gas keratopathy	19.6 (13–61)	NR	NR	90%	PKP, LK, DALK (numbers unspecified)	0	Prednisolone CsA MMF	Betamethasone 0.1%
Han et al, 2011[27]	III	24	CB, OCP, SJS, Mooren's ulcer, pterygium, pseudopterygium, exposure keratopathy	47.3 (17–114)	20/25 to LP	Range: 20/16 to NLP VA improved: 41.6% VA unchanged: 29.2% VA decreased: 29.2%	33.3%	45.8% PKP	45.8%	CsA Prednisolone (MMF—only for acute rejection and certain high-risk grafts)	Prednisolone acetate 1%
Eberwein et al, 2012[37]	III	20	Aniridia, CB, OCP, chronic ocular surface inflammation	20 (NR)	Mean VA ~20/400 15% ≥ 20/200	Mean 20/70 50% ≥ 20/200	70%	100% PKP 100% intraoperative MMC 0.02%	100%	Fluocortolone MMF CsA	Prednisolone acetate 1%
Baradaran-Rafii et al, 2013[26]	III	45	CB, SJS	26.1 (6–48)	20/2637	20/53 without PKP (excludes failed surgeries) 20/38 with subsequent PKP (excludes failed surgeries)	Repeat KLAL in 42.2% 73.4% survival at last follow-up including those requiring repeat KLAL	100% intraoperative MMC 0.02%	100% on recipient bed; 48% with AMT overlay	Prednisone MMF Tacrolimus	Betamethasone 0.1%
Parihar et al, 2017[29]	II	25	CB, SJS, OCP, chronic ocular allergy	12 (12)	≥20/200: 40% <20/200 to CF: 24% HM to LP: 36%	≥20/200: 64% < 20/200 to CF: 16% HM to LP: 20%	60%, no conjunctivalization 56%, no corneal neovascularization	NR	0	CsA	Prednisolone acetate 1%

(*Continued*)

Table 1. (Continued.)

Author(s) and Year	Level of Evidence	No. of Eyes	Etiology of LSCD	Mean (Range) Follow-up in Months	Preoperative BCVA	Postoperative BCVA	Survival (%)	Concurrent Corneal Procedures*	% Use of AMT	Postoperative Systemic Immunosuppression	Postoperative Topical Steroid/ Anti-inflammatory
Krysik et al, 2020[38]	III	43	CB, postinflammatory scar, post-traumatic scar, SJS	33 (10–60)	20/2000 to LP	53% gained ≥ 1 lines	61%	None	0	Methylprednisolone CsA MMF Azathioprine	Dexamethasone
Cheung et al, 2020[5]	III	224	Aniridia, CB, SJS, contact lens associated	86.4 (12–192)	Mean 20/1002	20/158 BCVA at final follow-up: 70% ≥ 2 lines improvement; 19% ≥ 20/40	64.7%	None	0	Tacrolimus MMF Prednisone	Lifitegrast 5% or CsA 0.05% Difluprednate or prednisolone acetate 1%
Li et al, 2022[39]	III	49	CB, rheumatism	46.8 (18–158)	≥ 20/200: 16%	44%: ≥ 20/200 69% ≥ 2 lines improvement at last follow-up	71.4%	51% DALK	0	Dexamethasone Prednisone	Prednisolone 1% Tacrolimus 0.1%

AMT = amniotic membrane transplantation; BCVA = best-corrected visual acuity; CB = corneal burn (chemical and/or thermal); CF = count fingers; CLAU = conjunctival limbal autograft; CsA = cyclosporin A; DALK = deep anterior lamellar keratoplasty; HM = hand motion; KLAL = keratolimbal allograft; LK = lamellar keratoplasty; LP = light perception; lr-CLAL = living-related conjunctival limbal allograft; LSCD = limbal stem cell deficiency; MMC = mitomycin C; MMF = mycophenolate mofetil; NLP = no light perception; NR = not reported; OCP = ocular cicatricial pemphigoid; PKP = penetrating keratoplasty; SJS = Stevens Johnson syndrome; VA = visual acuity.

*Does not include other surgeries such as cataract surgery, lid procedures, or forniceal reconstruction.

†Study does not differentiate follow-up duration among CLAU, lr-CLAL, and KLAL patients.

Evidence-Based Medicine.[20] A level I rating was assigned to well-designed and well-conducted randomized controlled clinical trials, a level II rating was assigned to well-designed case-controlled and cohort studies and randomized clinical trials with substantial methodologic deficits, and a level III rating was assigned to case series, case reports, and poor-quality cohort and case-controlled studies. Two studies were rated level II, and 19 studies were rated level III. There were no level I studies.

Published Results

Table 1 summarizes the studies on and outcomes of KLAL transplantation included in this assessment. The findings presented in Table 1 include reported preoperative best-corrected visual acuity (BCVA), postoperative BCVA, percentage survival of the grafts, any concurrent procedures performed at the time of KLAL and the use of amniotic membrane, and a brief summary of postoperative systemic and topical immunosuppressive therapy. Of note, postoperative systemic and topical immunosuppressive regimens were highly variable between the different studies, and there is no level I or II evidence comparing them; specific details on dosing and duration of therapies can be found in the articles referenced. Table 2 lists postoperative complications associated with KLAL transplantation, including ocular complications and complications associated with systemic immunosuppression. Table 3 presents the same set of data as Table 1 but for lr-CLAL studies, and Table 4 presents postoperative complications associated with lr-CLAL.

Visual Outcomes of KLAL

Mean follow-up duration for the studies included in this assessment ranged from 12 months to 95 months. Visual acuity was reported in 12 of the 14 articles reviewed for KLAL. Preoperative BCVA ranged from 20/25 to light perception, and postoperative BCVA ranged from 20/16 to no light perception. Eight studies evaluated the change in visual acuity at final follow-up after KLAL procedures, and 5 studies reported visual acuity as a percentage of eyes with vision improvement or as unchanged or decreased. The mean percentage of eyes demonstrating vision improvement was 59% (range, 42%–92%), vision unchanged was 29% (range, 17%–39%), and vision decrease was 18% (range, 8%–29%). Two articles reported the change in visual acuity over time, and it is notable that best visual acuity in these eyes did decline over time postoperatively. Solomon et al[21] (single-agent systemic immunosuppression, cyclosporine used) reported that at postoperative year 1, 77% of eyes had 20/200 BCVA or better. By 3 years, the percentage of eyes with 20/200 BCVA or better declined to 54% and by 5 years to 45%. Even in the course of the first 12 months, Wylegala et al[22] reported that improvement in BCVA declined from 54% to 35% between 6 months and 12 months postoperatively.

Table 2. Postoperative Complications Associated with Keratolimbal Allograft Transplantation

Author(s) and Year	No. of Eyes	Elevated IOP/Worsening Glaucoma (%)	Persistent Epithelial Defects (%)	Microbial Keratitis (%)	Corneal Melt or Perforation (%)	Acute Allograft Rejection Episode(s) (%)	Primary Graft Failure (%)	Complications from Systemic Immunosuppression
Solomon et al, 2002[21]	39	25.6	35.9	7.7	NR	NR	NR	NR
Ilari and Daya, 2002[23]	23	26.1	13	13	NR	39.4	24.2	NR
Maruyama-Hosoi et al, 2006[24]	85	33.1	NR	8.3	4.1	13.1	NR	NR
Liang et al, 2009[28]	12	NR	17	NR	NR	17	NR	10%, persistent hypertension and hyperbilirubinemia 10%, transient gastric upset and loss of appetite
Javadi et al, 2011[36]	40	NR	NR	NR	NR	10	NR	NR
Han et al, 2011[27]	24	37.5	33.3	16.7	8.3	41.7	12.5	NR
Eberwein et al, 2012[37]	20	5	20	NR	NR	10	NR	NR
Baradaran-Rafii et al, 2013[26]	45	17.8	26.7	8.9	2.2	17.8	11.1	NR
Parihar et al, 2017[29]	25	NR	32	8	4	4	4	Nausea/vomiting
Krysik et al, 2020[38]	43	58	14	NR	NR	7	7	NR
Cheung et al, 2020[5]	224	NR	NR	NR	NR	43.3	NR	NR
Li et al, 2022[39]	49	8.2	NR	18.4	6.1	18.4	NR	NR

IOP = intraocular pressure; NR = not reported.

Survival of KLAL

Survival of KLAL in the articles reviewed was highly variable, ranging from 21% to 90% survival at final follow-up (Table 1). Mean survival was 66% at 12 months (n = 9 studies), 63% at 24 months (n = 4 studies), 61% at 36 months (n = 5 studies), and 47% at 60 months (n = 2 studies) (Fig 1). Although the different studies defined the specifics of KLAL survival slightly differently, the basic common elements were the same. For this analysis, survival of KLAL is defined as maintaining normal corneal epithelial phenotype over the corneal edge of the grafted KLAL. Failure of the KLAL was determined by the presence of any of the following findings: diffuse, late fluorescein staining; progressive vascularization of the cornea through the limbus; persistent or recurrent epithelial defects with diffuse, persistent, irregular epithelium; or conjunctival goblet cells on the corneal surface by impression cytology.

Systemic immune suppression choice and duration may play a role in survival, especially in KLAL, where historically no ABO blood type and human leukocyte antigen (HLA) matching is performed. Ilari and Daya[23] found that there was a shorter KLAL survival time in patients not receiving systemic cyclosporin A. The underlying etiology of limbal stem cell failure may also impact outcomes. Both Maruyama-Hosoi et al[24] (cyclosporine with dexamethasone) and Solomon et al[21] found that patients with Stevens-Johnson syndrome had a worse prognosis with poorer visual outcomes and survival of KLAL. Maruyama-Hosoi et al[24] also found that patients with ocular cicatricial pemphigoid, mucous membrane pemphigoid, and chemical or thermal burns had a worse prognosis than patients with other etiologies for secondary stem cell deficiency.

The study by Cheung et al[5] (triple-agent systemic immunosuppression, prednisone, mycophenolate, and tacrolimus used), the largest and longest-term study included in this assessment, found a 65% overall survival of KLAL in eyes at last follow-up with a mean follow-up time of 7.9 ± 3.7 years (range, 1.0−15.0 years). However, based on findings from longitudinal studies, graft survival appears to decrease dramatically over time. Solomon et al[21] (single-agent cyclosporine used) reported a decrease in survival from 77% at 1 year postoperatively to 45% at 5 years postoperatively. That rate of survival is comparable to Wylegala et al,[22] who reported 59% at 3 years decreasing to 46% at 6 years (systemic immunosuppression regimen was not reported). Ilari and Daya[23] (cyclosporine and systemic corticosteroids used) reported lower survival rates with a decrease from 54% at 1 year to 27% at 3 years and 21% at final follow-up. Hong et al[25] reported that the rate of KLAL survival declines even within the first year postoperatively from 90% survival at 6 months down to 61% at 1 year.

Interestingly, Solomon et al[21] found that survival of a second KLAL in patients who underwent repeat surgery was better at 2 years postoperatively than with the primary KLAL; they speculate that postoperative measures to improve the ocular surface may have allowed for better outcomes of the second KLAL. Baradaran-Rafii et al[26] (triple-agent systemic immunosuppression, prednisone,

Table 3. Summary of Studies on and Outcomes of Living-Related Conjunctival Limbal Allograft Transplantation

Author(s) and Year	Level of Evidence	No. of Eyes	Etiology of LSCD	Mean (Range) Follow-up in Months	Preoperative BCVA	Postoperative BCVA	Survival (%)	Concurrent Corneal Procedures	% Use of Intraoperative AMT	Postoperative Systemic Immunosuppression	Postop Topical Steroid/Anti-inflammatory	Donor HLA Matched
Daya and Ilari 2001[40]	III	10	SJS, ectodermal dysplasia, CB, OCP, AKC	26.2 (17–43)	20/200 to HM	20/80 to HM VA improved: 70% VA unchanged: 30%	80%	None	0	Methylprednisolone Prednisone CsA	0.5% PF prednisolone CsA 2%	Yes: HLA, ABO
Samson et al, 2002[32]	III	10	SJS, AKC, Mooren's ulcer/Sjogren's	35 (29–51)	20/100 to LP	VA improved: 50% VA unchanged: 30% VA decreased: 10%	50%	None	20	Methotrexate Azathioprine CsA	Prednisolone acetate 1%	Yes: 87.5% HLA compatible
Santos et al, 2005[31,§]	II	23	CB, SJS	33 (NR)	Mean HM	Mean 20/275 VA improved: 60.6% VA unchanged: 30.3% VA decreased: 9.5%	40.0% @ 1 yr 33.3% @ 2 yrs 33.0% @ at mean follow-up 33 mos	48.5% keratoplasty	100	Prednisone CsA	Prednisolone acetate 1%	Yes: HLA 43.5% HLA compatible
Wylegala et al, 2008[22]	III	26	CB, OCP, SJS, postcryo, postinflammatory, aniridia	31.2* (6–72)	Mean 20/100	VA improved: 53.8% VA unchanged: 38.5% VA decreased: 7.7%	59.4% @ 3 yrs (includes 43 KLAL) 46.4% @ 6 yrs (includes 43 KLAL)	NR	NR	NR	NR	Yes: HLA
Scocco et al, 2008[33]	III	39	SJS, CB, Lyell's syndrome, ectodermal dysplasia, limbal tumors, multiple pterygium sx, OCP	48.7 (18–121)	NR	VA improved: 30.8%	33.3% required repeat lr-CLAL 84.6% @ 1 yr 79.5% @ final follow-up LK	2.6% PKP	17.9	None	NR	Yes: HLA (51.3% were haplo-identical)
Javadi et al, 2009[36]	III	25	Mustard gas keratopathy	37.2 (12–78)	Mean 20/448	Mean 20/132	100% @ 1 yr 80% @ final follow-up	20% PKP 8% LK	0	Prednisolone CsA	Betamethasone 0.1%	HLA and ABO not performed
Huang et al, 2011[41]	III	17	CB—partial stem cell deficiency (≤50%)	16.0 (12–26)	20/100–20/3333	20/29–20/200 VA improved: 100%	100%	None	17.6	Prednisone Dexamethasone	Dexamethasone	Yes: 76.5% HLA matched
El-Hofi and **Helaly** 2019[42]	III	20	CB	29.3 (18–42)	55% CF 45% HM	60% 20/200–20/400 40% CF	75%	None	0	Corticosteroids CsA	Prednisolone acetate 1%	Yes: HLA
Cheung et al, 2020[5]	III	63	Aniridia, CB, SJS, contact lens associated	60.0 (12–192)	Mean 20/678	20/100	82.5%	None	0	Tacrolimus MMF Prednisone	Lifitegrast 5% or CsA 0.05% Difluprednate or prednisolone acetate 1%	Yes: HLA, ABO

AKC = atopic keratoconjunctivitis; AMT = amniotic membrane transplantation; BCVA = best-corrected visual acuity; CB = corneal burn (chemical and/or thermal); CLAU = conjunctival limbal autograft; CsA = cyclosporin A; HLA = human leukocyte antigen; HM = hand motion; KLAL = keratolimbal allograft; LK = lamellar keratoplasty; LP = light perception; lr-CLAL = living-related conjunctival limbal allograft; LSCD = limbal stem cell deficiency; MMF = mycophenolate mofetil; NR = not reported OCP = ocular cicatricial pemphigoid; PF = preservative free; PKP = penetrating keratoplasty; SJS = Stevens Johnson syndrome; VA = visual acuity.
*Study does not differentiate follow-up duration among CLAU, lr-CLAL, and KLAL patients.

Table 4. Postoperative Complications Associated with Living-Related Conjunctival Limbal Allograft Transplantation

Author(s) and Year	No. of Eyes	Elevated IOP (%)	Persistent Epithelial Defects (%)	Microbial Keratitis (%)	Corneal Perforation/Melt (%)	Allograft Rejection Episodes (%)	Primary Graft Failure (%)
Daya and Ilari, 2001[40]	10	NR	20	NR	30	20	NR
Samson et al, 2002[32]	10	10	10	30	NR	20	NR
Santos et al, 2005[31],*	23	NR	NR	12	NR	13	NR
Wylegala et al, 2008[22]	26	NR	34.6	NR	NR	26.9	NR
Scocco et al, 2008[33]	39	NR	2.6	2.6	2.6	17.9	NR
Javadi and Baradaran-Rafii 2009[30]	25	12	4	4	NR	40	0
Huang et al, 2011[41]	17	NR	NR	NR	NR	17.6	NR
El-Hofi and Helaly, 2019[42]	20	35 (25% required Ahmed valve)	NR	NR	15	15	NR
Cheung et al, 2020[5]	63	NR	NR	NR	NR	30.2%	NR

IOP = intraocular pressure; NR = not reported.
*Unable to distinguish complication rates between CLAU and lr-CLAL groups.

mycophenolate, and tacrolimus used) also found that 73% of eyes were clinically successful at final follow-up with 42% of eyes having undergone at least 1 repeat KLAL, suggesting that repeat KLAL may be successful in certain cases of primary or late graft failure.

Complications Related to KLAL

Postoperative complications related to KLAL are listed in Table 2. The most common complications included elevated intraocular pressure (IOP) or worsening glaucoma, persistent epithelial defects, microbial keratitis, corneal

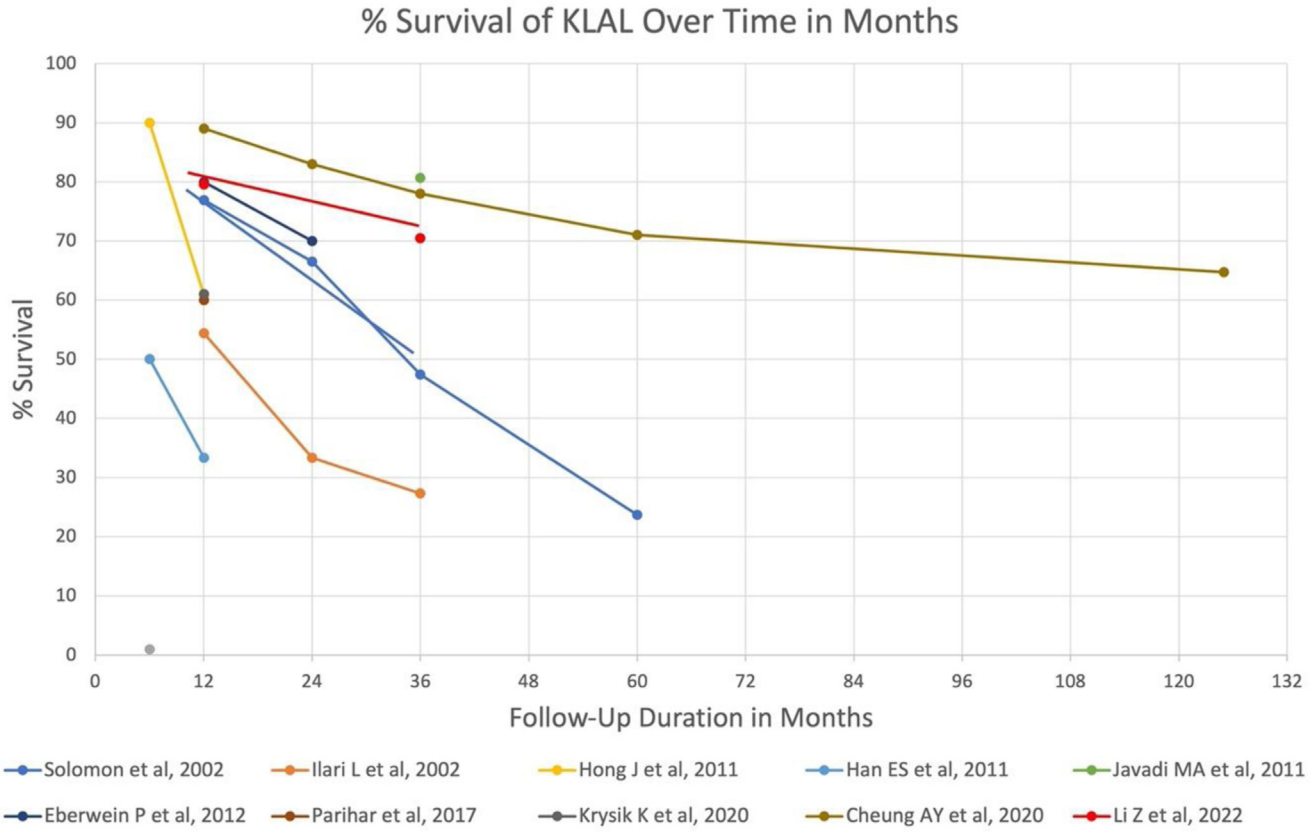

Figure 1. Percentage survival of keratolimbal allograft (KLAL) surgery over time. In 3 studies, survival data were given for only 1 time point.

melts or perforation, acute allograft immune rejection episodes, and primary graft failure.

Elevated IOP or worsening glaucoma was reported in 5% to 58% of eyes and typically addressed with topical therapy alone. Occasionally, patients required surgical intervention for glaucoma. Han et al[27] reported 3 of 22 eyes underwent tube shunt surgery or cyclophotocoagulation. Baradaran-Rafii et al[26] reported 6 of 8 eyes refractory to medical IOP-lowering therapy: Four eyes underwent a shunt procedure, 1 eye underwent cyclophotocoagulation, and 1 eye underwent cyclocryotherapy. Of note, some cases of elevated IOPs were also in eyes that had prior or subsequent penetrating keratoplasty procedures, which may have contributed to worsening glaucoma.[21] Many of these patients also had coexisting preoperative disease. Fortunately, it appears that worsening glaucoma only rarely resulted in complete loss of visual potential (2 eyes of 23 reported by Ilari and Daya[23]).

Persistent epithelial defects are defined as corneal epithelial defects lasting 2 or more weeks without resolution. These occurred in 13% to 36% of cases in the studies that were analyzed. More severe complications such as development of microbial keratitis or corneal melts and perforations were less common, occurring in 8% to 18% and 2% to 8% of eyes, respectively.

Acute allograft immune rejection episodes occurred in 4% to 43% of grafts. These episodes are characterized by the following clinical findings: epithelial defect in the limbal graft, acute edema/conjunctival chemosis in the area of the limbal graft, perilimbal and limbal vascular congestion, or engorgement around the limbal graft. Symptomatically, patients may have pain, photophobia, and sectoral conjunctival injection.

Primary allograft failure was defined as a refractory corneal epithelial defect persistent after KLAL or signs of allograft rejection unresponsive to treatment after KLAL. In the studies included in this assessment, primary graft failure occurred in 4% to 24% of cases.

Other less common postoperative complications that were reported in these studies include macular edema (1 eye),[21] retinal detachment (6 eyes),[21,24] vitreous hemorrhage, scleral thinning and staphyloma formation (2 eyes),[26] corneoscleral dellen formation,[26] epithelial cysts,[26] and graft hematoma.[26] In 2 eyes, it was reported that microbial keratitis of infected corneal grafts resulted in secondary severe tractional retinal detachments.[21]

Complications associated with systemic immunosuppression were also uncommon despite all KLAL patients being placed on some degree of systemic immunosuppression postoperatively. Postoperative systemic management included the use of any of the following medications: oral or intravenous steroids (methylprednisolone, prednisolone, prednisone, dexamethasone), cyclosporin A, mycophenolate mofetil, and tacrolimus. Liang et al[28] reported 1 patient with persistent hypertension and hyperbilirubinemia, which was reversed after discontinuation of tacrolimus. They also reported 1 patient with transient gastric upset and loss of appetite that resolved spontaneously. Parihar et al[29] also reported a few cases of nausea and vomiting associated with cyclosporin A, which were not clinically significant.

Visual Outcomes of lr-CLAL

Table 3 summarizes the studies included in this assessment related to lr-CLAL, including visual acuity outcomes and survival data. In general, the lr-CLAL studies that met the inclusion criteria for this assessment were smaller than those included for KLAL. Mean follow-up duration for these studies ranged from 16 months to 49 months. All 9 studies reported some degree of visual acuity improvement in patients, ranging from 31% to 100% of eyes having improvement of BCVA at final follow-up. Four studies reported BCVA unchanged in 30% to 39% of patients, and 3 studies reported a decline in BCVA in 8% to 10% of patients.

Survival of lr-CLAL

The survival rate of lr-CLAL ranged from 50% to 100% at final follow-up. In 8 of the 9 studies, HLA typing ± ABO blood typing was performed with donors chosen on the basis of the best match available, as shown in Table 3. The largest and longest-term lr-CLAL cohort reported by Cheung et al[5] (triple-agent systemic immunosuppression, prednisone, mycophenolate, and tacrolimus used) found an 82.5% overall survival of lr-CLAL eyes at last follow-up, with a mean follow-up time of 5.0 ± 3.1 years (range, 1.0−16.0 years). Only 2 studies reported survival of lr-CLAL over time. Javadi and Baradaran-Rafii[30] (cyclosporine and systemic corticosteroid used) reported 100% survival at 12 months, 77% survival at 36 months, and 51% survival at 60 months. Santos et al[31] (cyclosporine and systemic corticosteroid used) reported 44% survival at 12 months and 33% survival at 24 months. Of note, survival rate in the study by Santos et al may be lower than expected for lr-CLAL because these results include 43 KLAL procedures.

Complications Related to lr-CLAL

Postoperative complications related to lr-CLAL are summarized in Table 4. In general, fewer complications were reported with lr-CLAL than with KLAL procedures. Three of 8 studies reported elevated IOPs in 10% to 35% of eyes, with 1 study reporting a single case of end-stage glaucoma and progression to no light perception vision.[32] Five studies reported persistent epithelial defects in 3% to 35% of eyes. Microbial keratitis was reported in 3% to 30% of eyes in 4 studies, and corneal perforation/melts were reported in only 3 studies, ranging from 3% to 30% of eyes. There was 1 report of *Streptococcus pneumoniae* endophthalmitis occurring 1 week after lr-CLAL due to a persistent epithelial defect and secondary bacterial infection.[33]

Despite use of living-related donors, allograft rejection episodes were reported in all studies, ranging from 13% to 40% of eyes. However, there were no reported cases of primary graft failure in any of the studies.

Discussion

Bilateral LSCD is a devastating disease that can lead to severe vision impairment and corneal blindness in patients. Treatment options such as KLAL and lr-CLAL may provide some improvement of vision, but the results are mixed in terms of graft survival and vision improvement. This is likely due to KLAL and lr-CLAL surgeries for varied etiologies of LSCD being reported together (including various degrees of conjunctival deficiency), different regimens of systemic immunosuppression used, and historically no ABO blood type and HLA matching has been performed on KLAL donors. Additionally, preoperative confirmatory diagnostic testing for and staging of LSCD have not been well defined in many of these studies.

For both KLAL and lr-CLAL, patients with LSCD can experience improvement of vision. The percentage of eyes that experience an improvement in BCVA ranges from 42% to 92% in KLAL patients and 31% to 100% in r-CLAL patients. Survival ranges for KLAL and lr-CLAL are 21% to 90% and 33% to 100% in the 2 groups, respectively, in eyes with at least 1 year of follow-up. It is apparent from these numbers that the outcomes of the studies included in this assessment are highly variable, and determining a more generalizable conclusion on the overall success of these procedures may be difficult. There is tremendous variability between these studies with respect to specific criteria for defining success of the procedure, and the studies have varying preoperative recipient-donor matching criteria, surgical technique, follow-up periods, and postoperative treatment protocols (especially with respect to systemic immunosuppression regimens). Moreover, these data are predominantly from case series and should be interpreted with some caution. Patients should be counseled extensively preoperatively on the variability of outcomes from these procedures.

Fortunately, although survival of both KLAL and lrCLAL transplantation may decrease over time, the overall risk of devastating globe-threatening complications is rare. The most commonly reported complications include acute allograft rejection episodes, persistent epithelial defects, and microbial keratitis that may necessitate further surgical intervention but not loss of the eye. In the case of failure to restore the ocular surface with LSCT, these eyes could still be candidates for keratoprosthesis implantation or cultivated oral mucosal epithelial transplantation.[23,34] Patients undergoing lr-CLAL appear to have fewer reported postoperative complications, particularly with respect to elevations in IOP and primary graft failures. This may be associated with the fact that lr-CLAL patients were subjected to shorter periods of less intensive systemic immunosuppression and may be a reason to consider lr-CLAL over KLAL in patients when there is a suitable HLA-matched donor, particularly because risks to the donor are negligible.

Conclusions

The review of the literature suggests that both KLAL and lr-CLAL are viable options for patients with bilateral total LSCD. A triple-agent systemic immunosuppression protocol akin to solid organ transplantation demonstrated higher graft survival, especially for KLAL.[5] Given the limited options available for these patients, providing even several years of improved vision can be significant. Complications from systemic immunosuppression in these patients are relatively uncommon. Long-term survival likely requires increased systemic immunosuppression to minimize allograft rejection and graft failure. Further surgical interventions, including repeat grafts, may be necessary to maintain vision in this challenging population. Recent studies have shown that the outcomes for lr-CLAL are superior to KLAL due to a reduced rejection rate.

Future Research

Randomized controlled studies are needed to evaluate the long-term efficacy of both KLAL and lr-CLAL with a standardized criteria for staging LSCD before treatment and assessing outcomes of these surgeries. Future studies should use the diagnostic recommendation and staging system of LSCD as established by the Limbal Stem Cell Working Group to help with this standardization.[4] Evolving immunosuppression regimens along with ABO and HLA matching for deceased donors in KLAL have been reported in a small case series.[35] Thus, further work should be done to understand the optimal postoperative immunosuppression regimen for these patients, and a randomized controlled trial comparing regimens may be beneficial. Ultimately, future research on LSCT techniques will likely focus on autologous cultivated limbal epithelial transplantation for both bilateral and unilateral diseases in which a small amount of residual limbal stem cells is present. Further Ophthalmic Technology Assessments also may focus on cultivated allogenic limbal epithelial transplantation as an option for patients with bilateral total LSCD. Finally, identifying novel sources for corneal epithelial stem cells may provide additional options to addressing these challenging cases.

Footnotes and Disclosures

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Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **HLA** = human leukocyte antigen; **IOP** = intraocular pressure; **KLAL** = keratolimbal allograft; **lr-CLAL** = living-related conjunctival limbal allograft; **LSCD** = limbal stem cell deficiency; **LSCT** = limbal stem cell transplantation; **SLET** = simple limbal epithelial transplantation.

Keywords:
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