Systemic immunosuppression in limbal stem cell transplantation: best practices and future challenges

Brian G. Ballios, MD, PhD,[*] Maxwell Weisbrod, MD,[†] Clara C. Chan, MD,[*] Armand Borovik, MD,[‡] Jeffrey R. Schiff, MD,[§,‖] Kathryn J. Tinckam, MD, MMSc,[§,‖] Atul Humar, MD,[§] S. Joseph Kim, MD, PhD, MHS,[§,‖] Edward H. Cole, MD, MSc,[§,‖,¶] Allan R. Slomovic, MD, MSc[*,‡]

ABSTRACT •

The objective of this study was to evaluate systemic immunosuppression regimens used for patients undergoing ocular surface stem cell transplantation, including their benefits and adverse effects in the adjunctive management of limbal stem cell deficiency (LSCD). A systematic literature review was conducted using the MEDLINE and EMBASE databases (1980–2015). Data were collected on surgical intervention(s), type of immunosuppressive agent(s), duration of immunosuppression, percentage with stable ocular surface at last follow-up, mean follow-up time, and demographics. Data were also collected on adverse ocular and systemic outcomes. Sixteen reports met the inclusion criteria. There were no randomized controlled studies. Three studies were noncomparative prospective case series, whereas the majority were retrospective case series. Bilateral severe LSCD was the most common disease (50%), and keratolimbal allograft was the most common intervention (80%). Immunosuppressive regimens showed a progression from early studies using oral cyclosporine to later studies using combinations of mycophenolate mofetil and tacrolimus. Most studies included a course of high-dose systemic corticosteroids. For patients adherent to long-term systemic immunosuppression, stable ocular surface rates of 70%–80% at last follow-up were reported. Adverse effects included hypertension, diabetes mellitus, and biochemical abnormalities managed with pharmacotherapy or discontinuation of offending agents. There were no cases of mortality related to immunosuppression. However, the current literature does not elucidate which immunosuppressive regimen is most efficacious for different categories of LSCD or graft types. Evidence-based guidelines for systemic immunosuppression in limbal allograft therapy would benefit from randomized controlled and/or additional prospective studies. Long-term immunosuppression would benefit from close collaboration between ophthalmologists and transplant specialists to individualize treatments.

The limbus of the cornea contains a population of stem cells that are important for the proper maintenance and regeneration of the corneal epithelium.[1,2] Limbal stem cell deficiency (LSCD), caused by inherited or acquired disruption of this stem cell niche, results in poor corneal epithelialization and epithelial defects, secondary vascularization of the cornea, stromal scarring, and/or corneal conjunctivalization.[3] Etiologies include chemical or thermal burns; ocular cicatricial pemphigoid (OCP) and pseudo-OCP; aniridia; various forms of ectodermal dysplasia; Stevens–Johnson syndrome; contact lens injury; and iatrogenic injury during ocular surface surgery. These conditions may result in partial or total LSCD in the affected eye because of the degree of destruction of the limbus, conjunctival scarring, decreased tear film production, and the high risk of corneal keratinization. The patient will experience a number of distressing symptoms, including ocular pain, photophobia, and decreased vision. Before the 1980s, the few options for treatment of LSCD included lamellar (LKP) and penetrating keratoplasty (PK) with corneal transplantation, tarsorrhaphy, and artificial tears to maintain a corneal tear film.

Kenyon and Tseng[4] were the first to specifically transplant limbal stem cells in a conjunctival-limbal autograft from the contralateral eye; however, it was not until the mid-1990s that groups described the first keratolimbal allograft (KLAL) transplantations.[5,6] Since that time, the field has seen a remarkable proliferation and variation in the techniques of ocular surface stem cell transplantation (OSST),[7] often combined with PK or deep lamellar keratoplasty. In unilateral LSCD, tissue harvested from the contralateral eye may be used in an autograft.[4,8,9] In bilateral disease, which is more common, allogeneic donor material must be used.[10–14]

Systemic immunosuppression is critical for graft integration and survival after allograft transplantation.[15] Limbal allografts are at significantly higher risk of rejection than other more "central" corneal procedures involving the avascular stroma. In corneal transplantation, an avascular tissue is being transplanted into an avascular host site. In contrast, the limbus has a high concentration of tissue antigen-presenting cells (Langerhans' cells), which can trigger immunologic rejection[16] by T cells.[17] This may present as either acute allograft rejection with injection at the graft–host junction and conjunctivalization of the

https://doi.org/10.1016/j.jcjo.2017.10.040
ISSN 0008-4182/17

Canadian Ophthalmological Society | Société canadienne d'ophtalmologie
EYE PHYSICIANS AND SURGEONS OF CANADA | MÉDECINS ET CHIRURGIENS OPHTALMOLOGISTES DU CANADA

Table 1—Classification system for limbal allo-/autografts

Procedure	Abbreviation	Donor Site	Transplanted Tissue
Keratolimbal allograft	KLAL	Cadaver	Limbus/cornea
Conjunctival limbal autograft	CLAU	Contralateral eye	Limbus/conjunctiva
Living related conjunctival limbal allograft	lr-CLAL	Living relative	Limbus/conjunctiva

Adapted with permission from Daya et al.[19] and Holland and Schwartz.[20]

ocular surface or as chronic rejection characterized by slowly progressive conjunctivalization without evidence of acute inflammation.[18–20] It should be noted that the role of humoral immunity is not well defined in the context of the limbal allografts. The graft–host state in limbal transplantation must therefore be treated similarly to most cases of vascular solid organ transplants.

To our knowledge, no review with a significant focus on systemic immunosuppression and OSST has been undertaken in the past. Given the advances in transplantation technique and the large number of corneal specialists around the world engaged in OSST, it is timely to open a dialogue on the importance of establishing standard-of-care approaches to systemic immunosuppression. In this article, we look back at the literature around OSST to try to identify the evidence around best immunosuppression protocols and practices and to identify what data are needed and what opportunities exist for future study.

Methods

We systematically searched MEDLINE and EMBASE for articles addressing immunosuppressive protocols in OSST. The following MEDLINE subject heading (MeSH) terms were used: *cornea, stem cells, stem cell transplantation, humans, limbus corneae, immunosuppression,* and *immunosuppressive agents*. Reference lists were scanned to exclude reviews, letters, commentary, and animal and lab studies; only original articles were included. Searches were restricted to reports published between 1980 and 2015. We sought to include randomized control trials (RCTs), nonrandomized comparative studies, prospective or retrospective analyses, and case series involving at least 14 eyes, with precedent in the literature for studies reviewing surgical procedures for LSCD.[21] Studies included in the analysis needed to detail the immunosuppression protocols they used in the postoperative period.

Titles and abstracts were reviewed by one author (B.G.B.), and full-text articles that met the inclusion criteria were obtained. Two authors (B.G.B. and M.W.) extracted data using a standardized data collection form on surgical intervention(s), number of eyes, number of patients, type of immunosuppression (agents), duration of immunosuppression, mean time to successful tapering, percentage of patients tapered off immunosuppression, percentage with stable ocular surface at last follow-up, percentage nonadherent to therapy, mean follow-up time, and demographics including sex and mean age at surgery. The primary endpoints on which this review focused were mean follow-up time and percentage with stable ocular surface at last follow-up. Stable ocular surface was most often defined as an epithelialized corneal surface, absence of conjunctivalization of the cornea, and absence of perilimbal engorgement/vessel tortuosity. Discrepancies or disagreements were addressed by a second review by both authors and consensus. Formal meta-analytic techniques were not used because the studies were varied in terms of design and reported effect measures. Holland and Schwartz proposed a nomenclature and classification system[20] for OSST; we will use this system here (Table 1).

Two reviewers (B.G.B. and M.W.) independently assessed the studies that were included in the review according to a validated checklist for study quality used previously[22–24] (see Supplementary Data and Supplementary Tables 1 and 2, available online) and adapted from the Review Body for Interventional Procedures, which carries out reviews for the National Institutes of Health and Clinical Excellence ("Undertaking Systematic Reviews of Research on Effectiveness," CRD Report No. 4, 2001).

Results

The original literature search revealed 1444 articles related to *limbus corneae* (Fig. 1) (Supplementary Table 3, available online). After restricting the search to only those articles related to *immunosuppression* or *immunosuppressive agents* and excluding reviews, a title/abstract screen revealed that only 56 articles met the review criteria. Reviewing the full text, only 32 articles met our inclusion criteria based on study appropriateness and use of systemic immunosuppression. These articles were reviewed in detail, and a further 16 exclusions were made based on insufficient numbers of eyes in the study (<14), based on previous reviews of ocular surface therapy. A total of 16 reports were included in the final appraisal[13–15,25–37] (Table 2).

There were no published RCTs available for inclusion in our review. All studies involved patients on systemic immunosuppression after OSST surgery. Thirteen (81%) of 16 studies[15,25–31,33–37] were retrospective noncomparative case series or consecutive-subject cohort studies, whereas 3 were considered noncomparative prospective case series.[13,14,32] Five (31%) of 16 studies[13,26,28,29,33] looked at bilateral severe or total LSCD alone. No studies looked at only unilateral severe or total LSCD cases. Six