Challenges in the management of bilateral eyelid closure in Stevens-Johnson Syndrome

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Abstract

Purpose: To describe the challenges of surgically treating Stevens-Johnson syndrome (SJS) cases with bilateral eyelid closure, a serious ocular sequela.

Observations: This study involved two 69-year-old females, with subacute-stage SJS (Case 1 and Case 2), and a 37-year-old male with chronic-stage SJS (Case 3). Case 1 had undergone simultaneous bilateral symblepharon lysis at 4-months post SJS onset, and her logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity (VA) (BCVA) improved from 2.8 (both eyes) to 0.7 OD and 0.4 OS. Cases 2 and 3 underwent symblepharon lysis with intraoperative use of mitomycin C (MMC) and amniotic membrane transplantation (AMT) at 9 months (OD) and 11 months (OS) (Case 2) and at 31 years (OD) (Case 3) post SJS onset. At 3-months postoperative, Case 3 underwent cultivated oral mucosal epithelial sheet transplantation (COMET). In both cases, BCVA (logMAR) improved with the postoperative use of limbal-rigid contact lenses (CLs); i.e., from 2.8 to 0.5 OD and 1.2 OS (Case 2) and from 2.8 to 1.1 OD (Case 3). In all 5 treated eyes, eyelid opening and VA were maintained through final follow-up.

Conclusion and importance: In severe bilateral symblepharon cases, it can be difficult to predict postoperative outcomes, as proper surgical treatment is often delayed. In SJS cases with bilateral eyelid closure, the surgical intervention strategy of AMT and COMET, combined with limbal-rigid CL wear post surgery, can result in improved vision, and symblepharon surgery might be easier and possibly result in a better prognosis when performed at the early phase.

1. Introduction

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rare and severe cutaneous adverse-drug-reaction diseases which involve the skin and mucous membranes, and SJS and TEN differ only in the extent of epidermal detachment. In patients afflicted with SJS/TEN, the diversity of ocular involvement is reportedly characterized by conjunctiva hyperemia at the acute stage and severe ocular surface keratinization with symblepharon at the end stage.

The ocular surface changes in SJS/TEN are consisted of limbal stem cell deficiency (LSCD) and/or squamous metaplasia of the conjunctiva. Squamous metaplasia can be observed on the ocular surface, and due to an unclear mechanism, changes it to stratified, non-secretory, keratinized epithelium. As a sequelae, ocular surface changes in SJS/TEN have a high possibility for progression, especially in eyes with partial conjunctivalization and keratinization.

At the sub-acute and chronic stage of SJS/TEN, ophthalmologic examination can often reveal symblepharon, a partial or complete adhesion of the palpebral conjunctiva of the eyelid and the bulbar conjunctiva of the eyeball, or ankyloblepharon, a partial or complete fusion of the upper and lower eyelids. Depending on the location and severity of symblepharon, the pathological changes can alter the balance of the eye. In mild and moderate conditions, symblepharon can obstruct tear flow and the lacrimal duct, and alter the tear meniscus. Severe
symblepharon can result in decreased visual acuity (VA), restriction of ocular motility, and complete closure of the eyelid.\textsuperscript{11-13}

For the proper management of SJS/TEN-related ocular sequelae, surgical procedures for the correction of adnexal abnormalities, symblepharon release combined with amniotic membrane transplantation (AMT), and mucous membrane grafting (MMG) for lid-margin keratization, are often performed.\textsuperscript{4,5,14,15} Moreover, for the restoration of vision in SJS/TEN cases with severe ocular sequelae, previous studies have reported surgical interventions such as keratolimbal allograft (KLAL) or keratopethehelioplasty (KEP) followed with penetrating keratoplasty/keratoprosthesis, as well as non-surgical interventions such as scleral contact lens (CL) wear.\textsuperscript{4,5,16-18}

The purpose of symblepharon management is to overcome the pathological effect, and surgical treatment should be performed either before or during ocular surface reconstruction.\textsuperscript{13} Although various surgical methods have been proposed in previous studies for the successful management of symblepharon, the rate of recurrence widely ranges from 6.2\% to 40\%.\textsuperscript{5,14} Commonly, symblepharon lysis is performed, followed by ocular-surface reconstruction of the tarsal and bulbar conjunctiva with tissue substitutions, i.e., conjunctival tissue, an oral mucosal tissue graft, or AMT. To prevent re-attachment of the tissue surface, several surgical devices/procedures are used, such as a conformer, a symblepharon ring, a silicone sheet implant, additional application of a mitomycin C (MMC) or bevacizumb soaked sponge, or β-irradiation after surgery.\textsuperscript{11-13,20} We previously reported the use of cultivated oral mucosal epithelial sheet transplantation (COMET) in end-stage total limbal stem cell deficiency (LSCD) with symblepharon as a part of conjunctival fornix reconstruction, and the outcomes varied according to the underlying disease.\textsuperscript{21} Moreover, several other studies have reported performing COMET in SJS cases, yet the results have varied.\textsuperscript{19,22}

In cases of severe symblepharon resulting in eyelid closure, symblepharon surgery can produce critical improvement of VA. The patient’s VA can be further improved with the additional use of a CL post surgery. In SJS/TEN cases, the use of a scleral CL post surgery is mainly to reduce photophobia symptoms and improve vision.\textsuperscript{4} In SJS/TEN cases with ocular sequelae, visual rehabilitation post surgery using a limbal-ridg CL (Suncon Kyoto-CS\copyright; Sun Contact Lens Co., Ltd., Kyoto, Japan) reportedly improves VA better than spectacles, thus improving the patient’s quality of life (QOL).\textsuperscript{24,25} Moreover, other types of scleral CLs, such as those used prosthetic replacement of the ocular surface ecosystem (PROSE) lens, can reportedly improve vision in SJS patients.\textsuperscript{26-28}

The purpose of this present study was to describe the challenges of surgically releasing bilateral eyelid closure, a serious SJS-related ocular sequelae, and emphasize the importance of performing symblepharon surgery in bilateral eyelid closure to obtain improvement of VA.

## 2. Findings

The summary of the clinical data of all three cases is shown in Table 1.

### 2.1. Case 1

Case 1 involved a 69-year-old female who was referred to our hospital due to bilateral severe upper and lower eyelid adhesion. She had a history of SJS in March 2013 due to acetaminophen medication. Initial examination of the patient by a local ophthalmologist at 1-week post SJS onset revealed the adhesion of the upper and lower mucosal part of the eyelid in both eyes. It should be noted that since the patient lived in a rural location where new and follow-up examinations by local ophthalmologist were only available once per week, there was a delay in the management of her ocular condition at the acute stage. At 4-months post disease onset, the patient visited our hospital for further management. Upon examination, her logarithm of the minimum angle of resolution (logMAR) best-corrected VA (BCVA) was 2.8 in both eyes, and she was diagnosed with bilateral eyelid closure due to severe symblepharon (Fig. 1a, b, and 1e). Although we were unable to evaluate the details of the ophthalmological status, loose eye movement was detected via palpation. We performed bilateral symblepharon separation by use of a set of blunt-tip surgical scissors under local anesthesia. Post surgery, complete re-opening of the eyelids in both eyes without symblepharon was achieved, and the appearance of the cornea and ocular surface was good (Fig. 1c and d). Thus, we revised the diagnosis as bilateral ankyloblepharon. Post surgery, the patient’s VA dramatically improved to logMAR 0.3 OD and 0.5 OS, and betamethasone 0.1\% eye drops and sodium hyaluronate eye drops were administered every 3 hours. In addition, she was prescribed gatifloxacin 0.5\% eye drops 4-times daily and a 5 mg-per-day administration of oral prednisolone. The patient’s condition greatly improved with no conjunctivitis and bacteria colonization, and her final logMAR BCVA at 1-month postoperative was 0.7 OD and 0.4 OS.

### 2.2. Case 2

Case 2 involved a 69-year-old female who developed bilateral symblepharon with a VA of ‘light perception’ in March 2016 after being diagnosed with SJS 3 months previously. The causative drug was unknown, and she was subsequently referred to our department for eyelid reconstruction. Upon initial examination, bilateral upper-eyelid

| Case | Age | Gender | Laterality | Duration between SJS onset and surgery (months) | First surgery | Second surgery | Duration between surgery and LRCL placement (months) | Visual acuity preoperatively (logMAR) | Visual acuity on the last visit (logMAR) | Duration of follow-up after first surgery (months) |
|------|-----|--------|------------|-----------------------------------------------|---------------|---------------|-----------------------------------------------|----------------------------------|----------------------------------|-----------------------------------------------|
| 1    | 69  | Female | OD         | 4                                             | Ankyloblepharon lysis | No            | N/A                                          | 2.8                              | 0.7                              | 5                                             |
|      |     |        | OS         | 4                                             | Ankyloblepharon lysis | No            | N/A                                          | 2.8                              | 0.4                              | 5                                             |
| 2    | 69  | Female | OD         | 9                                             | Symblepharon lysis + MMC + AMT | No            | 2                                           | 2.8                              | 0.5                              | 29                                            |
|      |     |        | OS         | 11                                            | Symblepharon lysis + MMC + AMT | No            | 5                                           | 2.8                              | 1.2                              | 27                                            |
| 3    | 37  | Male   | OD         | 372                                           | Symblepharon lysis + MMC + AMT | COMET         | 3                                           | 2.8                              | 1.1                              | 69                                            |
|      |     |        | OS         | No surgery                                    | No             | No            | N/A                                          | 2.8                              | 2.8                              | N/A                                           |

OD = right eye; OS = left eye; MMC = Mitomycin C; AMT = amniotic membrane transplantation; COMET = cultivated oral mucosal epithelial sheet transplantation; LRCL = limbal rigid contact lens; N/A: not available.
symblepharon nearly covering the entire cornea surface was observed. In her right eye, there was no blockage of the lower lacrimal punctum (Fig. 2a, b, and 2e), and Schirmer test findings were 10 mm OD and 2 mm OS.

Eyelid reconstruction was postponed for 6 months due to the detection of Candida sp. and Methicillin-resistant coagulase-negative staphylococci from the conjunctival swab testing, and the patient was treated with a hospital pharmacy-made 0.1% fluconazole eye drops and vancomycin ophthalmic ointment 1%® (Toa Pharmaceutical Co., Ltd, Toyama, Japan). After a subsequent conjunctival swab test produced a negative finding, we performed eyelid and ocular surface reconstruction surgery on her right eye with AMT and a 4-min intraoperative sponge application of 0.04% MMC. Systemic steroids [i.e., betamethasone iv (2 mg/day) in combination with continuous oral betamethasone (1 mg/day) for 1 months] and cyclosporine 100mg/day were added to the postoperative treatment, and then tapered. Two months after the initial surgery, we performed the identical surgical method for symblepharon release in the patient’s left eye. In both eyes, limbal epithelium remained at the upper limbal area, and epithelial growth was observed from that area, ultimately resulting in complete epithelialization of the cornea.

Post surgery, limbal-rigid CL (Suncon Kyoto-CS®) were fitted in both eyes, i.e., in the right eye at 2-months postoperative and in the left eye at

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**Fig. 1.** The pre- and postoperative ophthalmological findings in Case 1. Images obtained at initial presentation showing the appearance of the patient’s right eye (1a) and left eye (1b). The patient underwent bilateral symblepharon surgical release simultaneously due to the patient’s social condition. An unexpected clear cornea with mild inflammation on the ocular surface was found in both eyes (1c, right eye; 1d, left eye). Schema illustrating the condition of each eye prior to surgery (1e).

**Fig. 2.** The pre- and postoperative ophthalmological findings in Case 2. Images showing the appearance of the patient’s right eye with an opened lower punctum (2a) and left eye (2b) prior to surgery. At 2.5-years postoperative, mild recurrence of symblepharon was observed in the right eye (2c). Successful symblepharon surgery resulted in maintaining a good postoperative outcome in the left eye with only mild cornea opacity (2d). Schema illustrating the condition of each eye prior to surgery (2e).
5-months postoperative, and her logMAR BCVA improved to 0.8 OD and 1.5 OS. The patient then underwent follow-up examinations with a local ophthalmologist. At 29-months postoperative, her final follow-up examination revealed a logMAR BCVA with CL of 0.5 OD and 1.2 OS (Fig. 2c and d).

2.3. Case 3

Case 3 involved a 37-year-old male with bilateral severe eyelid closure who was referred to our hospital in June 2014 for ocular reconstruction surgery (Fig. 3a, b, and 3e). He had previously experienced an onset of SJS at the age of 6 due to isopropylantipyrine, an anti-inflammatory medication. History taken from patient revealed his VA was relatively good (logMAR 0.3 in both eyes) at that time. However, he experienced bilateral repeated corneal erosion with dry eye, and his VA gradually decreased due to corneal haze. Subsequently, he was transferred to a school for children with disabilities from the age of 10. At 1-month post SJS onset, eyelid adhesion developed in his right eye, with severe symblepharon ultimately resulting in complete closure of the eyelids before the age of 20.

Surgical release of the symblepharon in the patient’s right eye was performed, and thick fibrous Tenons-capsule tissue was intensively removed until we were able to see the bare sclera. The patient then underwent ocular surface reconstruction using AMT, a 4-min intraoperative application of 0.04% MMC, and sutured KLAL transplantation. The administration of systemic anti-inflammatory drugs (a combination of prednisolone acetate and cyclosporine) accompanied the surgery.

Post surgery, the upper and lower fornix was well reconstructed, however, poor epithelialization was observed. A follow-up examination performed at 8-days postoperative, revealed that the limbal...

![Fig. 3. The pre- and postoperative ophthalmological findings in Case 3. Images showing total eyelid closure in the right eye (3a) and left eye (3b) prior to surgery. Right eye condition on the last follow-up (3c) and fitted with a limbal-rigid contact lens (Suncon Kyoto-CS®) to improve the visual acuity (VA) (3d). Schema illustrating the condition of the right eye prior to surgery (3e). Graph illustrating the change of right-eye VA from pre to post surgery, including the UCVA and BCVA after additional post-operative Suncon Kyoto-CS® lens wear (3f). UCVA: uncorrected visual acuity; BCVA: best corrected visual acuity; CS-lens: Suncon Kyoto-CS® limbal-rigid contact lens.](image-url)
transplantation epithelial graft on the patient’s right eye had dropped off and that there was inadequate graft-related epithelial cell growth. Thus COMET was subsequently performed on that eye via the previously described surgical technique and postoperative treatment course. Since the administration of systemic anti-inflammatory drugs is necessary to obtain an excellent outcome post surgery, the patient received intravenous administration of methylprednisolone 125 mg on the day of surgery, subsequently continued with prednisolone 2 mg/day for 3 days and cyclosporine 100 mg/day orally, and then tapered off.

At 3-months post COMET, the patient’s right-eye ocular surface was completely re-epithelialized and deemed stabilized, so he was fitted with a Suncon Kyoto-CS® limbal-rigid CL, and the VA in that eye gradually improved. At 4-years postoperative, his right-eye BCVA with the CL had improved to logMAR 1.1 (Fig. 3c–e).

3. Discussion

Bilateral severe symblepharon, which can develop into bilateral eyelid closure as a serious ocular sequela of SJS or TEN, is problematic for both the patient and the attending surgeon. The patient experiences limited ocular motility, thus greatly affecting the patient’s QOL. Moreover, attending physicians sometimes hesitate to perform the necessary treatment, as the surgical technique is difficult and the postoperative management is complicated. Bilateral severe symblepharon that develops into bilateral eyelid closure in SJS/TEN cases is extremely challenging, and there is currently no ‘gold standard’ symblepharon surgery for the treatment of cicatricial ocular surface disease.

The surgical methods applied for symblepharon are symblepharon release or lysis, then reconstruct the fornix with tissue substitution to prevent re-adhesion. Amniotic membrane is widely used as the substitute tissue for obtaining stable and transparent cornea epithelium. COMET has also been successfully used for conjunctival fornix reconstruction, as it results in complete re-epithelialization, ocular surface stabilization, and elimination of recurrence. 3,4

In cases of end-stage total LSCD, the ‘one-step’ method of symblepharon surgery combined with ocular surface reconstruction is one treatment option. Ocular surface reconstruction in SJS cases is challenging, and various surgical methods have previously been reported. Thoft introduced limbal stem cell transplantation or keratoepithelialplasty, and it can successfully be combined with symblepharon surgery. MMG is indicated in cases of lid-margin keratinization, which directly addresses the problem by surgically improving the surface of the posterior lid margin. In bilateral cases of total LSCD, Nakamura and associates reported successful outcomes when using COMET for obtaining stable and transparent cornea epithelium. COMET has also been successfully used for conjunctival fornix reconstruction, as it results in complete re-epithelialization, ocular surface stabilization, and elimination of recurrence.

In the 3 cases presented in this current study, various surgical strategies were performed, and the available options of AMT, MMC, and COMET provided us with the ability to perform the required surgeries in all 3 patients. In Case 1, the decision to perform ankyloblepharon lysis resulted in a stable cornea and an improved ocular surface, which was unexpected. This outcome may have been due to the patient being in the sub-acute stage of SJS. In Case 2, AMT and MMC provided good epithelialization post surgery, with the source of the epithelialization coming from the remaining small island of healthy limbal stem cells located at the superior region of the cornea in both eyes. In Case 3, COMET was the optimal choice to resolve the poor re-epithelialization following symblepharon surgery with AMT, MMC, and limbal allograft transplantation. This outcome was in line with the findings in a previous study that reported complete re-epithelialization and the prevention of recurrence post COMET surgery. The patient had a long history of SJS, and also long period of elapsed time between disease onset and when the required surgery was subsequently performed. This case illustrated that in SJS cases, long-term follow-up is vital, as severe ocular sequelae can gradually progress over time.

The management of bilateral LSCD requires surgical treatment that is followed by non-surgical therapeutic intervention (i.e., PROSE or the use of a Suncon Kyoto-CS® limbal-rigid CL). If remaining healthy epithelia is still available, AMT can be performed with MMC application. On the other hand, COMET, simple limbal epithelial transplantation (SLET), or KLAL shall be performed in situations in which no healthy epithelia remains. Both KLAL and SLET are reportedly beneficial for LSCD patients with mild to moderate conjunctival involvement. However, the cost of the preparation of the cultivated cells used for COMET is high.

It should be noted that tear function is an important factor for successful outcomes post ocular surface reconstruction surgery, as tears provide lubrication to the ocular surface and supply critical components such as vitamin A and epidermal growth factor. Thus, proper wound healing post surgery requires a good tear reflex to promote re-epithelialization.

The findings in a study by Yoshikawa and associates revealed that the ocular surface failures in chronic SJS/TEN cases kept progressing into total keratinization on long-term follow-up. Thus, surgeons might expect to perform repeated operations in this type of condition. Hence, we should consider performing symblepharon surgery as the ‘first-line treatment option’ for the management of severe ocular surface diseases, especially in cases of severe bilateral symblepharon. The use of limbal-rigid CLs for an extended period of time post symblepharon surgery might prevent symblepharon re-attachment, as the lens covers the corneal surface and possibly provides a barrier function to prevent micro-trauma to the cornea and conjunctiva. As reported by Itoi and associates, the lens acts as a rigid barrier that protects the cornea and reduces ocular pain. Moreover, limbal-rigid CL wear post surgery is known to help improve VA, thus greatly boosting the patient’s QOL. In addition, it has been reported that the use of PROSE lens in an SJS/TEN patient who had previously undergone surgical procedures resulted in a sustained and significantly large improvement of VA.

In all three cases, ophthalmologists did not involve in the initial management of the disease immediately post onset, the period in which ocular management is vital. The key point to predict the outcome of chronic stage SJS/TEN depends on a proper diagnosis and timing of the management with early intervention with AMT and/or steroid pulse therapy at the acute stage. Moreover, long-term postoperative follow-up is also mandatory for early detection of disease recurrence and for maintaining the visual prognosis.

4. Conclusions

Symblepharon surgery is often a necessary part of the required ocular surface reconstruction methods used for the optimal management of SJS/TEN-related ocular sequelae. Bilateral severe symblepharon with eyelid closure should take precedence when considering the proper treatment strategies, and early surgical intervention of symblepharon can present a better postoperative prognosis, thus improving the patient’s VA and overall QOL.

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Yulia Aziza: Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization.
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References
1. Harr T, French LE. Toxic epidermal necrolysis and Stevens-Johnson syndrome. *Orphanet J Rare Dis*. 2010;5:39.
2. Schwartz RA, McDonough PH, Lee BW. Toxic epidermal necrolysis: part I. introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. *J Am Acad Dermatol*. 2013;69(2):173. e1-13; quiz 85-86.
3. Bantugi-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau J-C. Clinical classification of cases of toxic epidermal necrosis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol*. 1995;129(1):92–96.
4. Jain R, Sharma N, Basu S, et al. Stevens-Johnson syndrome: the role of an ophthalmologist. *Surv Ophthalmol*. 2016;61(4):369–399.
5. Kohanim S, Palioura S, Saeed HN, et al. Acute and chronic ophthalmic involvement in Stevens-Johnson syndrome/toxic epidermal necrosis – comprehensive review and guide to therapy. Part II. Ophthalmic disease. *Ocul Surf*. 2016;14(20):168–188.
6. Liang L, Sheh H, Li J, et al. Limbal stem cell transplantation: new progresses and challenges. *Eye*. 2009;23(10):1946–1953.
7. Deng SX, Sejpal KD, Tang Q. Characterization of limbal stem cell deficiency by in vivo laser scanning confocal microscopy: a microstructural approach. *Arch Ophthalmol*. 2012;130(4):440–445.
8. Pungwiracharn V, Tseng SGC. Cytologic evidence of corneal diseases with limbal stem cell deficiency. *Ophthalmology*. 1995;102(10):1476–1485.
9. Yoshikawa Y, Ueta M, Fukunaka H, et al. Long-term progression of ocular surface disease in Stevens-Johnson syndrome and toxic epidermal necrosis. *Cornea*. 2020;39(6):745–753.
10. American Academy of Ophthalmology. Classification and management of eyelid disorders. In: *American Academy of Ophthalmology, Orbital, Eyelids, and Lacrimal System, Section 7, Basic and Clinical Science Course*. San Francisco, CA: American Academy of Ophthalmology; 2017:155–195.
11. Jain S, Rastogi A. Evaluation of the outcome of amniotic membrane transplantation for ocular surface reconstruction in spherophakia. *Eye*. 2004;18(12):1251–1257.
12. Zhao D, Yin HY, Cheng A, Shen R, Sheh H, Tseng S. Sealing of the gap between corneal limbal/conjunctival allograft for ocular surface reconstruction in Stevens-Johnson syndrome. *Arch Ophthalmol*. 2003;121(10):1369–1374.
13. Lee R, Khouei Z, Trikata E, et al. Long-term visual outcomes and complications of epithelial keratoplasty. *Cornea*. 2017;36(1):27–35.
14. Espina EM, Pasculle MD, Grueterich M, Solomon A, Tseng SGC. Keratolimbal allograft in corneal reconstruction. *Eye*. 2004;18:406–417.
15. Dan JK, Mehdi J, Chakravarty R, Solaimani R. Mucous membrane grafting for the post-Stevens-Johnson syndrome symblepharon: a case report. *Indian J Ophthalmol*. 2011;59(3):231–233.
16. Sotozono C, Inatomi T, Nakamura T, et al. Visual improvement after cultivated oral mucosal epithelial transplantation. *Ophthalmology*. 2012;119(2):193–200.
17. Venugopal R, Nappal R, Mohanty S, et al. Outcomes of cultivated oral mucosal epithelial transplantation in eyes with chronic Stevens-Johnson syndrome sequelae. *Am J Ophthalmol*. 2021;222:82–91.
18. Gopakumar V, Agarwal S, Srinivasan B, et al. Clinical outcome of autologous cultivated oral mucosal epithelial transplantation in ocular surface reconstruction. *Cornea*. 2019;38(10):1273–1279.
19. Sotozono C, Yamauchi N, Maeda S, et al. Tear exchangeable rigid contact lens for ocular sequelae resulting from Stevens-Johnson syndrome or toxic epidermal necrosis. *Am J Ophthalmol*. 2014;158:983–993.
20. Itou M, Ueta M, Ogino K, et al. Clinical trial to evaluate the therapeutic benefits of limbal-supported contact lens wear for ocular sequelae due to Stevens-Johnson syndrome/toxic epidermal necrosis. *Contact Lens Anterior Eye*. 2020;43(6):535–542.
21. Papakostas TD, Le HG, Chodosh J, et al. Prosthetic replacement of the ocular surface ecosystem as treatment for ocular surface disease in patients with a history of Stevens-Johnson syndrome/toxic epidermal necrosis. *Ophthalmology*. 2015;122(2):248–253.
22. Heur M, Bach D, Theophanous C, et al. Prosthetic replacement of the ocular surface ecosystem scleral lens therapy for patients with ocular symptoms of chronic Stevens-Johnson syndrome. *Am J Ophthalmol*. 2014;158(1):49–54.
23. Wang Y, Rao R, Jacobs DS, et al. Prosthetic replacement of the ocular surface ecosystem treatment for ocular surface disease in pediatric patients with Stevens-Johnson syndrome. *Am J Ophthalmol*. 2019;181:1–8.
24. Ariza Y, Inatomi T, Sotozono C, Kinoshita S. Pterygium excision with modified bare sclera technique combined with mitomycin C. *Jpn J Ophthalmol*. 2021;65(5):189–96.
25. Saif ATS, Khaleq MOA, Mahran WM. Role of amniotic membrane transplantation in symblepharon. *JOJ Ophthalmol*. 2016;1(3):555–565.
26. Jain S, Rastogi A. Evaluation of the outcome of amniotic membrane transplantation for ocular surface reconstruction in symblepharon. *Eye*. 2004;18(12):1251–1257.
27. Tseng SGC, Di Pascale MA, Liu DT, Gao YY, Baradan-Rafii A. Intraoperative mitomycin C and amniotic membrane transplantation for fornix reconstruction in severe cicatricial ocular surface diseases. *Ophthalmology*. 2005;112(5):896–903.
28. Shimazaki J, Shionoaki N, Tsutoba K. Transplantation of amniotic membrane and limbal autograft for patients with recurrent pterygium associated with pterygium. *Br J Ophthalmol*. 1996;80(2):235–240.
29. Honavar SG, Bansal AK, Sangwan VS, Rao GN. Amniotic membrane transplantation for ocular surface reconstruction in Stevens-Johnson syndrome. *Ophthalmology*. 2000;107(5):975–979.
30. Singh P, Singh A. Mitomycin-C use in ophthalmology. *JOSR J Pharm*. 2013(3):1–14.
31. Tsutoba K, Satake Y, Ohyama M, et al. Surgical reconstruction of the ocular surface in advanced ocular cicatricial pemphigoid and Stevens-Johnson syndrome. *Am J Ophthalmol*. 1996;122(3):368–72.
32. Rootman DB, Kim MJ, Aldave AJ. Ocular surface rehabilitation in Boston type I keratoprostheses with mucous membrane disease. *Ophthalmic Plast Reconstr Surg*. 2015;31(1):43–49.
33. Pu Y, Liu J, Tseng SGC. Oral mucosal graft to correct lid margin pathologic features in cicatricial ocular surface diseases. *Am J Ophthalmol*. 2011;152(4):600–608.
34. Thoft RA. Keratoprosthetics. *Am J Ophthalmol*. 1984;97(1):1–6.
35. Lee WR, Mannis MJ. Historical concepts of ocular surface disease. In: *Holland EJ, Mannis MJ, Lee WR, eds. Ocular Surface Disease: Cornea, Conjunctiva and Tear Film*. Philadelphia, PA: Elsevier; 2011:3–10.
36. Nakamura T, Takeda K, Inatomi T, Sotozono C, Kinoshita S. Long-term results of autologous cultivated oral mucosal epithelial transplantation in the scar phase of severe ocular surface disorders. *Br J Ophthalmol*. 2011;95(7):942–946.
37. Nakamura T, Inatomi T, Sotozono C, et al. Transplantation of cultivated autologous oral mucosal epithelial cells in patients with severe ocular surface disorders. *Br J Ophthalmol*. 2004;88(10):1280–1284.
38. Sotozono C, Inatomi T, Nakamura T, et al. Cultivated oral mucosal epithelial transplantation for persistent epithelial defect in severe ocular surface diseases with acute inflammatory activity. *Acta Ophthalmol*. 2014;92(6):447–453.
39. Komai S, Inatomi T, Nakamura T, et al. Long-term outcome of cultivated oral mucosal epithelial transplantation for fornix reconstruction in chronic cicatrising diseases. *Br J Ophthalmol*. 2021;105:1–8.
45. Sotozono C, Inatomi T, Nakamura T, et al. Oral mucosal epithelial transplantation and limbal-rigid contact lens: a therapeutic modality for the treatment of severe ocular surface disorders. Cornea. 2020;39(11):S19–S27.

46. Shanbhag SS, Patel CN, Goyal R, Donthineni PR, Singh V, Basu S. Simple limbal epithelial transplantation (SLET): review of indications, surgical technique, mechanism, outcomes, limitations, and impact. Indian J Ophthalmol. 2019 Aug;67(8):1265–1277.

47. Zhang Y, Lu XY, Hu RJ. Evaluation of artificial tears on cornea epithelium healing. Int J Ophthalmol. 2018;11(7):1096-1101.