Update on the application of amniotic membrane in immune-related ocular surface diseases

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Abstract:
Immune-related ocular surface diseases, a group of diseases in which immune dysregulation damages the ocular surface, can induce uncontrolled inflammation and persistent epithelial defect, thus leading to the most severe forms of acute keratoconjunctivitis, dry eye disease, epithelial keratitis, stromal ulceration, and corneal perforation. As these diseases are often refractory to treatments, they have a threatening impact on the vision and life quality of patients. This review summarizes the current literature regarding the clinical application of sutured and self-retained cryopreserved amniotic membrane (AM) in treating Stevens–Johnson syndrome/toxic epidermal necrolysis, ocular graft-versus-host disease, Sjögren's syndrome, Mooren's ulcer, and peripheral ulcerative keratitis. Current evidence supports the safety and effectiveness of AM, especially self-retained cryopreserved AM, in decreasing ocular surface inflammation, promoting corneal epithelial and stromal healing, improving visual acuity, and preventing sight-threatening complications. Future studies are still required to validate the above findings and explore the varied application methods of AM to improve the clinical efficacy in maintaining ocular surface health.

Keywords:
Amniotic membrane, stevens–Johnson syndrome, graft-versus-host disease, mooren's ulcer, peripheral ulcerative keratitis

Introduction

The immune system is like a double-edged sword. When everything goes well, it protects humankind from disease; however, when things go awry, it becomes a nightmare rampaging in our bodies, causing unimaginable harm. Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) is such a case in point. Once triggered, the immune dysregulation can attack skin and mucous membranes, resulting in a spectrum of vesiculobullous disorders.[1,2] In general, 40%–84% of SJS/TEN patients will experience ocular symptoms during the acute phase,[3] whereas 21%–59% of the survivors will be burdened with its chronic ocular sequelae.[4] An early intervention is essential in precluding the severe visual impairment and the chronic sequelae of SJS/TEN.

Since first described in 2002 by John et al.,[5] the amniotic membrane (AM) has been increasingly employed in the management of acute-phase SJS/TEN due to its epithelializing, anti-inflammatory, anti-scarring, and immunomodulatory features.[3,6] The emerging clinical evidence evinces that the timely application of AM after disease onset in acute SJS/TEN appears to result in significant clinical benefits, including a better recovery in best-corrected visual acuity (BCVA), more stable ocular surface, and less ocular cicatricial sequelae.[3,7-9] Amniotic membrane transplantation (AMT) has also proved to be a viable alternative method in ocular surface reconstruction during the chronic
phase of SJS/TEN\[^{10,11}\]\}. Furthermore, the application of AM is well suited not only in the management of SJS/TEN but also to other immune-related conditions such as ocular graft-versus-host disease (oGVHD), Sjögren’s syndrome (SS), Mooren’s ulcer, and peripheral ulcerative keratitis (PUK).

Our literature review of the PubMed\(^\text{®}\) and Web of Science\(^\text{TM}\) databases published before January in 2021 reveals the evidence on the application of AM in immune-related ocular surface diseases. Literature retrieval was conducted using the following keywords: amniotic membrane, Stevens–Johnson syndrome, toxic epidermal necrolysis, ocular graft-versus-host disease, Sjögren’s syndrome, Mooren’s ulcer, and peripheral ulcerative keratitis. This review summarizes literature evidence about how AM is applied in immune-related ocular surface diseases and how sight-threatening complications can be prevented by AMT.

Properties of Amniotic Membrane and Update on Amniotic Membrane Transplantation Method

AM, the innermost layer of the placenta, is a thin, semi-transparent, and avascular tissue, which consists of a monolayered epithelium, a thick basement membrane, and an avascular stroma.\[^{12-14}\]\ AM provides mechanical support and contains many growth factors such as epidermal growth factor, keratinocyte growth factor, hepatocyte growth factor, and nerve growth factor, all of which help promote the adhesion and migration of epithelial cells in the ocular surface.\[^{13,14}\]\ AM can reduce inflammation in the ocular surface by suppressing the expression of pro-inflammatory cytokines as well as release anti-inflammatory cytokines.\[^{14-16}\]\ AM may be a source of stem cells, which are reported to have the immunomodulatory properties on both the innate and adaptive immune systems.\[^{16}\]\ AM inhibits the expression of transforming growth factor-β to reduce scar formation.\[^{14,17}\]\ In addition, AM may have antiangiogenic and antibacterial effects.\[^{14,16,18}\]

The employment of AMT in ophthalmology was first introduced in ocular surface reconstruction by Kim and Tseng in 1995.\[^{19}\]\ Since then, AMT has been widely applied in the treatment of a range of ocular surface disorders, including chemical and thermal injuries, persistent epithelial defects (PEDs), corneal ulcers, ocular surface reconstruction after resection of pterygia, ocular surface tumors, symblephara, neurotrophic keratopathies, and immune-mediated ocular surface diseases including SJS/TEN, oGVHD, and SS.\[^{13,14,18,20-24}\]

The application method for AMT depends on the depth, size, and area of the affected ocular surface and corneal lesion/s, including inlay/graft AMT with epithelial-side-up amnion to replace lost stromal tissue, onlay/patch AMT where amnion is placed epithelial-side-down over the wound periphery as a temporary biological dressing, or combinatorial/sandwich AMT.\[^{16,25}\]\ AMT can be performed with a sutured or sutureless method.\[^{14}\]\ The application of sutureless AMT can aid patient care at the bedside or in an office setting. The self-retained cryopreserved AM, ProKera\(^\text{®}\) (Bio-Tissue, Inc., Miami, FL, USA), is a sheet of AM fused to a dual symblepharon ring system.\[^{14}\]\ After instillation of anesthetic eye drops, ProKera\(^\text{®}\) can be easily inserted onto the patient’s eye without sutures in a way similar to a contact lens, but unlike a contact lens, it has the added benefit of AM’s biological actions for suppressing inflammation and promoting healing.\[^{26}\]

Clinical Evidence of Amniotic Membrane Transplantation in Acute Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis

In the acute stage of SJS/TEN, defined as the first 2 months after onset of symptoms,\[^{27}\]\ the inflammatory reaction attacks the ocular surface characterized by eyelid margin inflammation, conjunctival pseudomembrane formation, and epithelial defects of the cornea and the conjunctiva.\[^{2,28}\]\ If the ocular surface inflammation and epithelial lesions are not promptly managed, the inflammatory process tends to be prolonged and results in limbal stem cell deficiency (LSCD) and ocular surface scarring.\[^{2}\]\ Considering the widespread “cytokine storm,” early control of the destructive inflammation in the acute phase can prevent the long-term ophthalmologic problems.\[^{9,27}\]\ Topical and intravenous (IV) corticosteroids are one means; however, topical steroids alone may not be sufficient in severe cases and systemic steroids have been controversial due to concerns over possible increased mortality.\[^{9}\]\ Moreover, topical steroids have poor tolerance, such as delayed healing, increased risk of infection, and steroid-related high intraocular pressure after prolonged use.

The emerging clinical evidence from randomized control trials (RCTs), case–control studies, and case reports\[^{29,31}\]\ demonstrates that AMT combined with medication therapy as early in the clinical course of SJS/TEN plays a significant part in the production of better clinical outcomes, including superior visual outcome and limitation of ocular cicatricial sequelae. Patients with greater than Sotozono’s Grade 2 ocular involvement (either ocular surface epithelial defect or pseudomembrane formation) are advised to receive AMT.\[^{32}\]\ Table 1 summarizes AMT for managing acute SJS/TEN. Most cases received AMT 2 weeks after the symptom onset. The earliest application day reported...
| Authors and publishing year | Study type | Number of patients (eyes) | Mean age, years (SD/range) | Ratio of children to adult | Severity at presentation, n (%) | AMT method (%) |
|-----------------------------|------------|--------------------------|---------------------------|---------------------------|--------------------------------|----------------|
| Sharma et al., 2016[7]      | RCT        | AMT + medicine: 25 (50)  | 31.69 (16.67)             | NA                        | Mild: 88% Moderate: 12%        | Fibrin glue with a symblepharon ring |
| Gregory, 2011[33]           | PSA        | 10 (20)                  | 16.2 (3-28)               | NA                        | Severe                        | Suture/ProKera |
| Shanbhag et al., 2020[34]   | RS         | 29 (55)                  | 23 (6-69)                 | 10:19                     | NA                            | Suture (3/55, 56%) ProKera (2/55, 44%) |
| Yang et al., 2020[35]       | RS         | 16 (32)                  | 27.2 (21.5)               | 7:9                       | 25/32 very severe 7/32 severe | Suture |
| Shanbhag et al., 2019[36]   | RS         | 48 (96)                  | 29.1 (18/1.5-71)          | 13:26                     | Mild 22% Severe 54% Very severe 24% | Suture/ProKera |
| Ahmad et al., 2017[37]      | RS         | SJS: 32                  | 10 (1-16)                 | NA                        | NA                            | Suture/ProKera/both |
| Agrawal and Pratap, 2015[38]| RS         | Non-SJS: 16              | 6 (0.03-14)               | NA                        | Sutureless AM mounted on symblepharon conformer |
| Ma et al., 2015[39]         | RS         | 9 (18)                   | 6-18                      | NA                        | NA                            | AMT with multiple pieces/one large single piece |
| Kim et al., 2013[40]        | RS         | 51                       | Pediatric group: 7.5 (4.8/1-16) Adult group: 46.2 (14.2/21-59) | 17:34 | NA | Pediatric group: AMT 2/AMT + medicine 2 Adult group: AMT 0/AMT + medicine 5 |
| Hsu et al., 2012[41]        | RS         | AM group: 13 (25)        | 2-82                      | NA                        | Severe: 20.3% Moderate: 20.3% Mild: 38.5% | Suture/ProKera |
| Shamas et al., 2010[42]     | RS         | MT group: 17 (33)        | 2-82                      | NA                        | Suture/ProKera/AM with 24 mm Kontur bandage contact lens |
| Shay et al., 2009[43]       | Review     | 8 (16)                   | 2-82                      | 3:5                       | Severe                        | Suture/ProKera/AM with 24 mm Kontur bandage contact lens |
| Nassim et al., 2021[44]     | Case report| 1 (2)                    | 8 weeks                   | NA                        | Severe                        | Cryopreserved AM: 4 |
| Elhusseiny et al., 2021[45] | Case report| 1 (2)                    | 2 months                  | NA                        | Severe                        | Suture |
| Baş and Uçakhan Gündüz, 2019[46] | Case report| 1 (2)                    | 1                         | NA                        | Severe                        | Sutureless with symblepharon ring |
| Cheung et al., 2016[47]     | Case report| 1 (2)                    | 61                        | NA                        | Severe                        | Sutureless with symblepharon ring and fibrin glue |
| Pruett et al., 2014[48]     | Case report| 1 (2)                    | 27                        | NA                        | Severe                        | Sutureless with symblepharon ring and fibrin glue |
| Muqit et al., 2007[49]      | Case report| 1 (2)                    | 10                        | NA                        | Severe                        | Suture |

Contd...
| Authors and publish year | Application time of symptom onset | BCVA outcome after AMT | Ocular cicatricial sequelae | Follow-up |
|--------------------------|-----------------------------------|------------------------|-----------------------------|-----------|
| Sharma et al., 2015<sup>[7]</sup> | Within 1-4 weeks | AMT group: 0.068±0.10 logMAR units | No cases in AMT group | 6 |
| Gregory, 2011<sup>[33]</sup> | 3-10 days | All ≥20/30 | Mild-to-moderate cicatricial sequelae | ≥6 months |
| Shanbhag et al., 2020<sup>[3]</sup> | 5 days | 87% (48/55) of eyes ≥20/40 | 78% (43/55): MGD | 2.5 (1.2-3.6) years |
| Yang et al., 2020<sup>[34]</sup> | 5.5 (range: 1-30) | 21/32 (65%) of eyes ≥20/40 | Trichiasis, lid margin keratinization, lid entropion, LSCD, distichiasis, dry eye | 36±35 months |
| Shanbhag et al., 2019<sup>[37]</sup> | 66% within 7 days | 92% in AMT group BCVA ≥20/40 | 17% in AMT group | 2.6 years |
| Ahmad et al., 2017<sup>[30]</sup> | 2-14 days | 86.9% SJS ≥20/40 | 7% | NA |
| Agrawal and Pratap, 2015<sup>[36]</sup> | NA | NA | NA | NA |
| Ma et al., 2015<sup>[38]</sup> | NA | All ≥20/40 | Formation of symblephara to be less | 2-24 months |
| Kim et al., 2013<sup>[39]</sup> | NA | Mean logMAR significantly improved in adult and pediatric group | A significant improvement in adult group | NA |
| Hsu et al., 2012<sup>[40]</sup> | Within 2 weeks | Poor outcomes: 7.1% in early AMT group: 38.9% in MT group | Moderate and severe group | Early AMT: 13.6 months |
| Shammas et al., 2010<sup>[41]</sup> | 4-12 days | 4 patients >20/40 | 5 patients | Mean 7.7 months |
| Shay et al., 2009<sup>[2]</sup> | Within 3 days to 2 weeks | All ≥20/40 | No LSCD, 2/12 symblepharon, 6/12 corneal peripheral vascularization | 9 (4-36) months |
| Nassim et al., 2021<sup>[42]</sup> | 8 days | NA | Intermittent presence of mucus on the ocular surface | NA |
| Elhusseini et al., 2021<sup>[43]</sup> | 5 days | NA | No signs of ocular sequelae | NA |
| Baş and Uçakhan Gündüz, 2019<sup>[44]</sup> | 3 days | NA | No signs of ocular sequelae | 2 years |
| Cheung et al., 2016<sup>[45]</sup> | 8 days | 20/20 OD 20/25 OS | Mild symblephara/MGD | 4 months |
| Pruett et al., 2014<sup>[46]</sup> | 5 days | 20/20 OU | Mild symblephara | 2 months |
| Muqtet et al., 2007<sup>[47]</sup> | NA | NA | No signs of ocular sequelae | 6 months |

SD=Standard deviation, BCVA=Best-corrected visual acuity, AMT=Amniotic membrane transplantation, RCT=Randomized control trial, NA=Not applicable, PS=Prospective study, RS=Retrospective study, MGD=Meibomian gland disease, LSCD=Limbal stem cell deficiency, SJS=Stevens-Johnson syndrome, AM=Amniotic membrane, MT=Membrane transplantation, OD=Right eye, OS=Left eye, OU=Both eyes
is 1 day.\textsuperscript{[34]} In a RCT, 72\% of mild-to-moderate SJS patients (18/25) sought treatment within 1 week of the symptoms, of whom 92\% (23/25) within the first 48 h in the AMT combined with medication group reported no statistically significant loss of vision and no cases had ocular cicatricial sequelae at the end of 6 months while the only medication therapy group experienced a reduction in BCVA and a higher ratio of complications with corneal haze occurring in 44\%, corneal vascularization and conjunctivalization in 24\%, and symblepharon in 16\% of eyes.\textsuperscript{[7]} In a recent retrospective cohort study for long-term outcomes (median follow-up of 2.5 years) of AM use, all 55 eyes received their first AMT at a median interval of 5 days after onset of skin rash, and 87\% of eyes (48/55) had a BCVA 2.0/40; however, eyelid-related complications and dry eyes remain a common problem even with the use of AM.\textsuperscript{[3]} The outcome of BCVA in a majority of patients (50\%–100\%) can reach more than 20/40 after early AM treatment.\textsuperscript{[2,3,7,33,39]} Evidence also reveals that delayed AMT is associated with worse BCVA and ocular surface outcome. In a retrospective cohort study from Yang \textit{et al}., three patients had late AMT in 13, 19, and 30 days, respectively; the four eyes of them had BCVA B 20/400 and all developed significant chronic sequelae such as LSCD, limiting visual outcome.\textsuperscript{[34]} A similar outcome was also presented in case–control studies from Gregory\textsuperscript{[33]} and Hsu \textit{et al}.\textsuperscript{[8]}

Early involvement of ophthalmologists or easy-applied AMT by nonophthalmologist in the acute stage can ensure optimal timing of AMT. In some conditions, patients may not receive prompt ophthalmic consultation as soon as possible. Considered as a dermatological emergency, SJS/TEN is associated with a high mortality rate of up to 35\% in adults and up to 17\% in children.\textsuperscript{[34,45]} Most patients were admitted to the intensive care unit (ICU) or emergency room (ER) after the initial symptom onset.\textsuperscript{[3,34]} AMTs were frequently performed at the bedside. A majority of patients required multiple AMTs. Reasons for AMT delay were found to include severe systemic disease, delay in transfer from another facility, delay in diagnosis from dermatology, or consent and child custody issues due to parental refusal.\textsuperscript{[34]} Studies show that pediatric patients tend to have more severe ocular involvement,\textsuperscript{[34,38,44]} and may benefit from earlier intervention with AMT. The study from Basu \textit{et al}. showed 99\% of 568 eyes in 284 children patients of acute SJS had no prior AM grafting, and 60\% of these eyes had low-vision or blindness leaving over.\textsuperscript{[44]} Therefore, an easy-applied AMT, such as ProKera\textsuperscript{®} without systemic sedation, is a valid option for nonophthalmic physicians to use at bedside even in the ICU, especially in pediatric patients or patients in severe systemic conditions.

AMT can be applied in a suture or sutureless method, which has both its advantages and disadvantages. At the acute phase of SJS/TEN, it is critical to completely cover the entire ocular surface including the lid margin in order to prevent entire epithelial damage. AMT can restore adequate bulbar surface and fornix depth and prevents recurrence of symblepharon in severe cases of SJS.\textsuperscript{[43]} The suture method was described previously. The cryopreserved AM is covered to the globe surface, fornices, and tarsal conjunctiva by the use of a symblepharon ring, either commercial or custom made from IV extension tubing, and then sutured to the upper and lower eyelids to assure coverage of the eyelid margins. Partial AM coverage of the ocular surface may not serve to minimize the cicatrizing ocular sequelae of SJS and TEN as effectively as complete coverage.\textsuperscript{[39]} Although ProKera\textsuperscript{®} only covers the cornea and surrounding bulbar conjunctiva, leaving the rest of the conjunctiva, fornices, and eyelid margins exposed, its advantages include easy bedside insertion without sedation and easy replacement if the membrane melts.\textsuperscript{[37]} Mild and moderated SJS patients can be initially treated with ProKera\textsuperscript{®}. Severe SJS/TEN patients can be initially treated with ProKera\textsuperscript{®} at the bedside due to the poor systemic condition or the difficulty in sutures without an operating microscope, until the AMT surgery could be performed. Alternatively, the AM can be fixated to the lid margin using cyanoacrylate glue. Using this method, it is easier to perform the procedure in the ICU or ER.\textsuperscript{[46]} The application of AMT is safe and the reported complications including microbial infection, hemorrhage beneath the amnion, and detachment of the membrane are at low risk.

Clinical Evidence of Amniotic Membrane Transplantation in Chronic Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis

30\%–50\% of patients with acute SJS/TEN will go on to develop chronic cicatrical ocular sequelae, including lid margin keratinization, trichiasis, entropion, progressive symblepharon, dry eye disease (DED), corneal pannus, and PED.\textsuperscript{[28]} AMT combined with corneal limbal graft, conjunctival autograft, mucous membrane graft, and lamellar keratoplasty has been used in the corneal and conjunctival surface construction of chronic SJS/TEN, for indication of PED, corneal ulcer, symblepharon, and pseudopterygium.\textsuperscript{[14,28,47]}

AMT can successfully reconstruct the conjunctiva and fornix, although some severe cases have failure of construction and recurrence of symblepharon.\textsuperscript{[50]} In a study from Tseng \textit{et al}., complete fornix reconstruction was demonstrated in 12 of 17 eyes (70.6\%) using AMT combined with the use of mitomycin C, whereas 2 eyes had a partial success, and 3 eyes (three patients)
had recurrence of symblepharon with restricted motility.\textsuperscript{[11]}

**Clinical Evidence of Amniotic Membrane Transplantation in Ocular Graft-Versus-Host Disease**

oGvHD is a devastating immune-mediated complication of allogeneic hematopoietic stem cell transplantation (HSCT).\textsuperscript{[31]} Pseudomembranous conjunctivitis with corneal epithelial sloughing can be observed in acute GvHD within the first 100 days following HSCT.\textsuperscript{[52]} The common ocular manifestation of chronic oGvHD is DED or keratoconjunctivitis sicca, which may contribute to PED.\textsuperscript{[53,54]} Artificial tears, topical immunosuppressants, corticosteroids, autologous serum, punctal occlusion, and contact lenses have been used in promoting healing and managing inflammation in oGvHD.\textsuperscript{[60]} However, in a subset of oGvHD patients, dryness and inflammation of the ocular surface can be refractory to treatment, ultimately resulting in serious complications, including corneal ulceration and corneal perforation.

Based on the biological features of AM, sutured AM or ProKera\textsuperscript{®} has also been used to treat severe refractory oGvHD for indications of severe dry eye, corneal PED, ulceration, and perforation.\textsuperscript{[55-59]} In a recent case report, a 69-year-old male of oGvHD presented with diffuse conjunctival inflammation, severe superficial punctate keratitis, and PED on the right eye worse than the left eye; ProKera\textsuperscript{®} was applied in the right eye while artificial tears, topical corticosteroids, and bandage contact lens were continued in the left eye. One-month post-AM placement, the right eye remained asymptomatic and the visual acuity improved to 20/30 without any additional therapy, whereas the left eye improved to 20/70 with the medicine treatment.\textsuperscript{[59]} In some severe cases, AM can seal tiny corneal perforation so that keratoplasty can be avoided.\textsuperscript{[96,97]} Nevertheless, early intervention with AM in oGvHD can significantly prevent serious complications such as corneal ulceration and perforation.\textsuperscript{[56]}

**Clinical Evidence of Amniotic Membrane Transplantation in Sjogren’s Syndrome**

SS is an autoimmune disorder that mainly affects exocrine glands such as the lacrimal and salivary glands, resulting in a loss of tear and saliva production.\textsuperscript{[56,61]} The ocular manifestations include severe keratoconjunctivitis sicca, recurrent epithelial erosion, nonhealing corneal ulcers, and even corneal perforation.\textsuperscript{[61]} Current therapies include artificial tears, topical anti-inflammatory and immunosuppressive eye drops, bandage contact lenses, scleral contact lenses, autologous serum drops, punctal occlusion, and systemic treatment, which help to improve the signs and symptoms of ocular dryness.\textsuperscript{[60]} In cases that are refractory to standard therapies, the use of ProKera\textsuperscript{®} is beneficial in the improvement of symptoms and ocular surface staining in patients with SS.\textsuperscript{[62]} Moreover, AM can promote the healing of corneal melting and ulceration.\textsuperscript{[63,64]} The inflammation in immune-related DED is more severe and progressive than nonimmune-related DED. This is why conventional anti-inflammatory agents generally fail to resolve the symptoms and signs of DED.\textsuperscript{[65]} Cheng and Tseng et al. reported a case of successful treatment of rheumatoid arthritis-related refractory DED in a 48-year-old female by ProKera\textsuperscript{®} in conjunction with conventional and systemic immunotherapy. The patient finally achieved visual acuity improvement from 20/400 to 20/70 in the right eye and from 20/100 to 20/30 in the left eye.\textsuperscript{[65]}

**Clinical Evidence of Amniotic Membrane Transplantation in Mooren’s Ulcer, Peripheral Ulcerative Keratitis, and Other Immune-Related Ocular Surface Diseases**

AMT or AMT combined with corneal or conjunctival grafts has also been used in Mooren’s ulcer, PUK, and other immune-related PED with or without corneal ulcer and perforation.\textsuperscript{[66-73]} PUK is a group of corneal disorders that cause peripheral corneal thinning, usually associated with systemic autoimmune diseases,\textsuperscript{[74]} while Mooren’s ulcer is an idiopathic, noninfectious, painful, and progressive PUK which is thought to be an autoimmune disease in the absence of any diagnosable systemic disorder.\textsuperscript{[75]} The management should start from an accurate diagnosis by ruling out bacterial, fungal, or *Acanthamoeba* infections.\textsuperscript{[71]} Single or multilayer AMT can assist the healing of nonresponsive Mooren’s ulcers and PUK with decreased inflammation, leading to a good visual outcome and a low frequency of recurrence.\textsuperscript{[66-69]} In the study from Ngan and Chau, the mean time to complete epithelialization after AMT in eyes of Mooren’s ulcers was 12.4 ± 5.2 days, with 10 of 13 eyes receiving localized AMT having a final visual acuity of 6/12 or better.\textsuperscript{[69]} The study from Schallenberg et al. showed that although AMT was not able to cure severe forms of Mooren’s ulcer, it was still able to support the immunosuppressive therapy in acute situations such as corneal thinning.\textsuperscript{[76]} In the study from Jia et al., corneal ulcers in all 12 patients (12 eyes) of severe PUK with endothelial exudates healed by 1–2 weeks after AMT combined with topical corticosteroids and anterior chamber washout; all patients achieved a stable ocular surface with no recurrence during follow-up.\textsuperscript{[71]}

**Conclusion**

The treatment of immune-related ocular surface disorders...
remains challenging due to its complex immune responses. Current clinical evidence supports the notion that both sutured and self-retained cryopreserved AM treatment modalities can successfully be employed to treat uncontrolled inflammation-related epithelial defect, corneal ulceration, perforation, and ocular cicatricial sequelae in SJS/TEN, 

gVHD, SS, Mooren’s ulcer, and PUK. The prompt application of AMT in severe cases significantly accelerates the restoration of vision and ocular surface health in patients. It is crucial that consulting ophthalmologists have an awareness of AMT as an effective treatment option. Considering that there is a wide array of AM-derived products, the clinical application of AM should not be confined to its current modalities. The development of AM-derived eye drops or gels shows much promise.[16,77] Future studies are required to explore the varied application methods of AM to improve clinical efficacy in maintaining ocular surface health.

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Conflicts of interest
The authors declare that there are no conflicts of interests of this paper.

References

1. Power WJ, Ghoraishiri M, Merayo-Lloves J, Neves RA, Foster CS. Analysis of the acute ophthalmic manifestations of the erythema multiforme/Stevens-Johnson syndrome/toxic epidermal necrosis disease spectrum. Ophthalmology 1995;102:1669-76.
2. Shaya E, Kheirkhah A, Liang L, Sheha H, Gregory DG, Tseng SC. Amniotic membrane transplantation as a new therapy for the acute ocular manifestations of Stevens-Johnson syndrome and toxic epidermal necrosis. Surv Ophthalmol 2009;54:686-96.
3. Shanbhag SS, Hall I, Chodosh J, Saeed HN. Long-term outcomes of amniotic membrane treatment in acute Stevens-Johnson syndrome/toxic epidermal necrosis. Ocul Surf 2020;18:517-22.
4. Catt CJ, Hamilton GM, Fish J, Mireskandari K, Ali A. Ocular manifestations of Stevens-Johnson syndrome and toxic epidermal necrosis in children. Am J Ophthalmol 2016;166:68-75.
5. John T, Foulks GN, John ME, Chong K, Hu D. Amniotic membrane in the surgical management of acute toxic epidermal necrosis. Ophthalmology 2002;109:351-60.
6. Walkden A. Amniotic membrane transplantation in ophthalmology: An updated perspective. Clin Ophthalmol 2020;14:2057-72.
7. Sharma N, Thenarasun SA, Kaur M, Pushker N, Khanna N, Agarwal T, et al. Adjuvant role of amniotic membrane transplantation in acute ocular Stevens-Johnson syndrome: A randomized control trial. Ophthalmology 2016;123:484-91.
8. Hsu M, Jayaram A, Verner R, Lin A, Bouchard C. Indications and outcomes of amniotic membrane transplantation in the management of acute Stevens-Johnson syndrome and toxic epidermal necrosis: A case-control study. Cornea 2012;31:1394-402.
9. Ciraksky JB, Sippel KC, Gregory DG. Current ophthalmologic treatment strategies for acute and chronic Stevens-Johnson syndrome and toxic epidermal necrosis. Curr Opin Ophthalmol 2013;24:321-8.
10. Gomes JA, Santos MS, Ventura AS, Donato WB, Cunha MC, Höflling-Lima AL. Amniotic membrane with living related corneal limbal/conjunctival allograft for ocular surface reconstruction in Stevens-Johnson syndrome. Arch Ophthalmol 2003;121:1369-74.
11. Tseng SC, Di Pascale MA, Liu DT, Gao YY, Baradaran-Rafii A. Intraoperative mitomycin C and amniotic membrane transplantation for fornix reconstruction in severe cicatricial ocular surface diseases. Ophthalmology 2005;112:896-903.
12. Le Q, Deng SX. The application of human amniotic membrane in the surgical management of limbal stem cell deficiency. Ocul Surf 2019;17:221-9.
13. Mead OG, Tighe S, Tseng SCC. Amniotic membrane transplantation for managing dry eye and neurotrophic keratitis. Taiwan J Ophthalmol 2020;10:13-21.
14. Liu J, Sheha H, Fu Y, Liang L, Tseng SC. Update on amniotic membrane transplantation. Expert Rev Ophthalmol 2010;5:645-61.
15. Solomon A, Rosenblatt M, Monroy D, Ji Z, Pflugfelder SC, Tseng SC. Suppression of interleukin 1alpha and interleukin 1beta in human limbal epithelial cells cultured on the amniotic membrane stromal matrix. Br J Ophthalmol 2001;85:444-9.
16. Riboh JC, Saltzman BM, Yanke AB, Cole BJ. Human amniotic membrane-derived products in medicine: Basic science, early results, and potential clinical applications. Am J Sports Med 2016;44:2425-34.
17. Lee SB, Li DQ, Tan DT, Meller DC, Tseng SC. Suppression of TGF-beta signaling in both normal conjunctival fibroblasts and pterygial body fibroblasts by amniotic membrane. Curr Eye Res 2000;20:325-34.
18. Gomes JA, Romano A, Santos MS, Dua HS. Amniotic membrane use in ophthalmology. Curr Opin Ophthalmol 2005;16:233-40.
19. Kim JC, Tseng SC. Transplantation of preserved human amniotic membrane for surface reconstruction in severely damaged rabbit corneas. Cornea 1995;14:473-84.
20. Meller D, Pires RT, Mack RJ, Figueiredo F, Heiligenhaus A, Park WC, et al. Amniotic membrane transplantation for acute chemical or thermal burns. Ophthalmology 2000;107:980-9.
21. Brooks D, Mead OG, Tighe S, Tseng SC. Self-retained cryopreserved amniotic membrane for the management of corneal ulcers. Clin Ophthalmol 2020;14:1437-43.
22. Lee SH, Tseng SC. Amniotic membrane transplantation for persistent epithelial defects with ulceration. Am J Ophthalmol 1997;123:303-12.
23. Tseng SC, Prabhatawat P, Lee SH. Amniotic membrane transplantation for conjunctival surface reconstruction. Am J Ophthalmol 1997;124:765-74.
24. Solomon A, Pires RT, Tseng SC. Amniotic membrane transplantation after extensive removal of primary and recurrent pterygia. Ophthalmology 2001;108:449-60.
25. Meller D, Paulkin M, Thomasen H, Westekemper H, Steuhl KP. Amniotic membrane transplantation in the human eye. Dtsch Arztebl Int 2011;108:243-8.
26. Shaya E, Khadem JJ, Tseng SC. Efficacy and limitation of sutureless amniotic membrane transplantation for acute toxic epidermal necrosis. Cornea 2010;29:359-61.
27. Shanbhag SS, Rashad R, Chodosh J, Saeed HN. Long-term effect of a treatment protocol for acute ocular involvement in Stevens-Johnson syndrome/toxic epidermal necrosis. Am J Ophthalmol 2019;208:331-41.
28. Kohanim S, Palioula S, Saeed HN, Akpek EK, Amsesua G, Basu S, et al. Acute and chronic ophthalmic involvement in Stevens-Johnson syndrome/toxic epidermal necrosis – A comprehensive review and guide to therapy. II. Ophthalmic disease. Ocul Surf 2016;14:168-88.
29. Muqit MM, Ellingham RB, Daniel C. Technique of amniotic membrane transplant dressing in the management of acute Stevens-Johnson syndrome. Br J Ophthalmol 2007;91:1536.
30. Pruet CM, Queen JH, Kim G. Amnion doughnut: A novel method for sutureless fixation of amniotic membrane to the bulbar and palpebral conjunctiva in acute ocular-involving Stevens-Johnson syndrome. Cornea 2014;33:1240-4.

31. Nassim JS, Karim SA, Grenier PO, Schmidt B, Jones KM. Infantile toxic epidermal necrolysis: Successful treatment of an 8-week-old with intravenous immunoglobulin and amniotic membrane transplant. Pediatr Dermatol 2021;38:202-5.

32. Sottoluzo C, Ueta M, Nakatani E, Kitami A, Watanabe H, Sueki H, et al. Predictive factors associated with acute ocular involvement in Stevens-Johnson syndrome and toxic epidermal necrolysis. Am J Ophthalmol 2015;160:228-37.e2.

33. Gregory DG. Treatment of acute Stevens-Johnson syndrome and toxic epidermal necrolysis using amniotic membrane: A review of 10 consecutive cases. Ophthalmology 2011;118:908-14.

34. Yang Y, Fung SS, Chew H, Mireskandari K, Ali A. Amniotic membrane transplantation for Stevens-Johnson syndrome/toxic epidermal necrolysis: the Toronto experience. Br J Ophthalmol 2020;1-6. bjophthalmol-2020-316056.

35. Ahmad MS, Frank GS, Hink EM, Palestine AG, Gregory DG, McCourt EA. Amniotic membrane transplants in the pediatric population. J AAPOS 2017;21:215-8.

36. Agrawal A, Pratap VB. Amniotic membrane transplantation (AMT) without the use of sutures/fibrin glue. Nepal J Ophthalmol 2015;7:173-7.

37. Ma KN, Thanos A, Chodosh J, Shah AS, Mantagos IS. A novel technique for amniotic membrane transplantation in patients with acute Stevens-Johnson syndrome. Ocul Surf 2016;14:31-6.

38. Kim KH, Park SW, Kim MK, Wee WR. Effect of age and early intervention with a systemic steroid, intravenous immunoglobulin or amniotic membrane transplantation on the ocular outcomes of patients with Stevens-Johnson syndrome. Korean J Ophthalmol 2013;27:331-40.

39. Shammas MC, Lai EC, Sarkar JS, Yang J, Starr CE, Sippel KC. Management of acute Stevens-Johnson syndrome and toxic epidermal necrosis utilizing amniotic membrane and topical corticosteroids. Am J Ophthalmol 2010;149:203-13.e2.

40. Elhusseiny AM, Gise R, Scelfo C, Mantagos IS. Amniotic membrane transplantation in a 2-month-old infant with toxic epidermal necrolysis. Am J Ophthalmol Case Rep 2021;21:101017.

41. Bağ Z, Üçakhan Güdüz Ö. Sutureless amniotic membrane transplantation in a pediatric patient with acute toxic epidermal necrolysis Turk J Ophthalmol 2019;49:356-60.

42. Cheung CS, Ali A, Chew HF. Successful treatment of acute ocular-involving toxic epidermal necrolysis using amniotic membrane suture fixed to custom designed symblepharon rings. Cornea 2016;35:578-81.

43. Saeed HN, Chodosh J. Ocular manifestations of Stevens-Johnson syndrome and their management. Curr Opin Ophthalmol 2016;27:522-9.

44. Basu S, Shanbhag SS, Gokani A, Kedar R, Bahuguna C, Sangwan VS. Chronic ocular sequelae of Stevens-Johnson syndrome in children: Long-term impact of appropriate therapy on natural history of disease. Am J Ophthalmol 2018;189:17-28.

45. Honavar SG, Bansal AK, Sangwan VS, Rao GN. Anniotic membrane transplantation for ocular surface reconstruction in Stevens-Johnson syndrome. Ophthalmology 2000;107:975-9.

46. Shanbhag SS, Chodosh J, Saeed HN. Sutureless amniotic membrane transplantation with cyanoacrylate glue for acute Stevens-Johnson syndrome/toxic epidermal necrolysis. Ocul Surf 2019;17:560-4.

47. Hick S, Demers PE, Brunette I, La C, Mabon M, Duchesne B. Amniotic membrane transplantation and fibrin glue in the management of corneal ulcers and perforations: A review of 33 cases. Cornea 2005;24:369-77.

48. Zhao D, Yin HY, Cheng A, Chen R, Sheha H, Tseng SC. Sealing of the gap between the conjunctiva and tenon capsule to improve symblepharon surgery. Am J Ophthalmol 2015;160:438-60.

49. Heiriklah A, Ghaffari R, Kaghazkanani R, Hashemi H, Behrouz MJ, Raja VK. A combined approach of amniotic membrane and oral mucosa transplantation for fornix reconstruction in severe symblepharon. Cornea 2013;32:155-60.

50. Solomon A, Espana EM, Tseng SC. Amniotic membrane transplantation for reconstruction of the conjunctival fornices. Ophthalmology 2003;110:93-100.

51. Jagasia MH, Greinix HT, Arora M, Williams KM, Wolff D, Cowen EW, et al. National institutes of health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 2015;21:389-401.e1.

52. Shikari H, Antin JH, Dana R. Ocular graft-versus-host-disease: A review. Surv Ophthalmol 2013;58:233-51.

53. Sinha S, Singh RB, Dohlan TH, Wang M, Taketani Y, Yin J, et al. Prevalence of persistent corneal epithelial defects in chronic ocular graft-versus-host disease. Am J Ophthalmol 2020;218:296-303.

54. Giannaccare G, Pellegrini M, Bernabei F, Scocchia V, Campos E. Ocular surface alterations in ocular graft-versus-host disease: All the pieces of the complex puzzle. Graefes Arch Clin Exp Ophthalmol 2019;257:1341-51.

55. Yin HY, Dhanireddy S, Weisenthal R, Swan R, Alpert S, Cheng AM. Self-retained cryopreserved amniotic membrane in treating acute ocular graft-versus-host-disease (oGVHD). Am J Ophthalmol Case Rep 2020;19:100761.

56. Peric Z, Skegro I, Durakovici N, Desnica L, Pulanic D, Serventi-Seiwerth R, et al. Amniotic membrane transplantation-a new approach to crossing the HLA barriers in the treatment of refractory ocular graft-versus-host disease. Bone Marrow Transplant 2018;53:1466-9.

57. Peris-Martínez C, Menezes JL, Díaz-Llopis M, Aviño-Martínez JA, Navea-Tejerina A, Risueño-Reguillo P. Multilayer amniotic membrane transplantation in severe ocular graft versus host disease. Eur J Ophthalmol 2001;11:183-6.

58. Yeh PT, Hou YC, Lin WC, Wang II, Hu FR. Recurrent corneal perforation and acute calcareous corneal degeneration in chronic graft-versus-host disease. J Formos Med Assoc 2006;105:334-9.

59. Mohammadpour M, Maleki S, Hashemi H, Beheshtnejad AH. Recurrent corneal perforation due to chronic graft versus host disease; a clinicopathologic report. J Ophthalmic Vis Res 2016;11:108-11.

60. Bjordal O, Norheim KB, Redahl E, Jonsson R, Omdal R. Primary Sjögren’s syndrome and the eye. Surv Ophthalmol 2020;65:119-32.

61. Akpek EK, Bunya YV, Saldanha JI. Sjögren’s syndrome: More than just dry eye. Cornea 2019;38:558-61.

62. Shafer B, Fuerst NM, Massaro-Giordano M, Palladino V, Givnish M, Macchi I, et al. The use of self-retained, cryopreserved amniotic membrane for the treatment of Sjögren syndrome: A case series. Digit J Ophthalmol 2019;25:21-5.

63. Tu PN, Hou YC. Bilateral corneal melting associated with topical corticosteroids/fibrin glue. Eur J Ophthalmol 2001;11:108-11.

64. Perret B, Fuerst NM, Massaro-Giordano M, Palladino V, Givnish M, Macchi I, et al. The use of self-retained, cryopreserved amniotic membrane for the treatment of Sjögren syndrome: A case series. Dig J Ophthalmol 2019;25:21-5.

65. Tu PN, Hou YC. Bilateral corneal melting associated with topical corticosteroids/fibrin glue. Eur J Ophthalmol 2001;11:108-11.

66. Bergerud M, Mameletzi E, Nicolas M, Rivier D, Majo F. Long-term follow-up of multilayer amniotic membrane transplantation (MLAMT) for non-traumatic corneal perforations or deep ulcers with descemetocele. Klin Monbl Augenheilkd 2013;230:413-8.

67. Cheng AM, Tighe S, Sheha H, Tseng SC. Adjunctive role of self-retained cryopreserved amniotic membrane in treating immune-related dry eye disease. Int Ophthalmol 2018;38:2219-22.

68. Hanada K, Shimazaki J, Shimamura S, Tsukuba O, Multilayered amniotic membrane transplantation for severe ulceration of the cornea and sclera. Am J Ophthalmol 2001;131:324-31.

69. Solomon A, Meller D, Prabhasawat P, John T, Espana EM, Steuhl KP, et al. Amniotic membrane grafts for nontraumatic
corneal perforations, descemetoceles, and deep ulcers. Ophthalmology 2002;109:694-703.

68. Chen KH, Hsu WM, Liang CK. Relapsing Mooren’s ulcer after amniotic membrane transplantation combined with conjunctival autografting. Ophthalmology 2004;111:792-5.

69. Ngan ND, Chau HT. Amniotic membrane transplantation for Mooren’s ulcer. Clin Exp Ophthalmol 2011;39:386-92.

70. Prabhasawat P, Tesavibul N, Komolsuradej W. Single and multilayer amniotic membrane transplantation for persistent corneal epithelial defect with and without stromal thinning and perforation. Br J Ophthalmol 2001;85:1455-63.

71. Jia Y, Gao H, Li S, Shi W. Combined anterior chamber washout, amniotic membrane transplantation, and topical use of corticosteroids for severe peripheral ulcerative keratitis. Cornea 2014;33:559-64.

72. Ke L, Shen D, Wang H, Qiao C, Zeng Q. Lamellar keratoplasty combined with amniotic membrane transplantation for the treatment of corneal perforations: A clinical and in vivo confocal microscopy study. Biomed Res Int 2020;2020:7403842.

73. Mishra AV, Cadieux DC, Gjerde H, Lewis DR. Peripheral ulcerative keratitis secondary to atypical hemolytic Uremic syndrome. Cornea 2020;39:1431-2.

74. Gupta DY, Kishore DA, Kumari DP, Balakrishnan DN, Lomi DN, Gupta DN, et al. Peripheral ulcerative keratitis. Surv Ophthalmol 2021;S0039-6257(21)00067-9.

75. Kafkala C, Choi J, Zafirakis P, Baltatzis S, Livir-Rallatos C, Rojas B, et al. Mooren ulcer: An immunopathologic study. Cornea 2006;25:667-73.

76. Schallenberg M, Westekemper H, Steuhl KP, Meller D. Amniotic membrane transplantation ineffective as additional therapy in patients with aggressive Mooren’s ulcer. BMC Ophthalmol 2013;13:81.

77. Murri MS, Moshirfar M, Birdsong OC, Ronquillo YC, Ding Y, Hoopes PC. Amniotic membrane extract and eye drops: A review of literature and clinical application. Clin Ophthalmol 2018;12:1105-12.