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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

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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), Sjogren's syndrome (SS), Mooren's ulcer, and peripheral ulcerative keratitis (PUK).

Our literature review of the PubMed® and Web of Science™ 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, Sjogren'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.[2,6,18,20-24]

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.[6,25] 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® (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® 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

Table 1: Amniotic membrane transplantation for managing acute Stevens-Johnson syndrome/toxic epidermal necrolysis

Authors and publish 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) Single medicine: 25 (50)	31.69 (16.67) 27.92 (12.48)	NA	Mild: 88% Moderate: 12%	Fibrin glue with a symblepharon ring
Gregory, 2011[33]	PS	10 (20)	16.2 (3-28)	5:5	Severe	Suture/ProKera
Shanbhag *et al.*, 2020[3]	RS	29 (55)	23 (6-69)	10:19	NA	Suture (31/55, 56%) ProKera (24/55, 44%)
Yang *et al.*, 2020[34]	RS	16 (32)	27.2 (21.5)	7:9	25/32 very severe 7/32 severe	Suture
Shanbhag *et al.*, 2019[27]	RS	48 (96)	29.1 (18.7/1.5-71)	13:26	Mild 22% Severe 54% Very severe 24%	Suture/ProKera
Ahmad *et al.*, 2017[35]	RS	SJS: 32 Non-SJS: 16	10 (1-16) 6 (0.03-14)	NA	NA	Suture/ProKera/both
Agrawal and Pratap, 2015[36]	RS	8 (14)	34 (25-46)	NA		Sutureless AM mounted on symblepharon conformer
Ma *et al.*, 2016[37]	RS	9 (18)	6-18	NA	NA	AMT with multiple pieces/one large single piece
Kim *et al.*, 2013[38]	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[8]	RS	AM group: 13 (25) MT group: 17 (33)	NA	NA	Severe: 20.3% Moderate: 20.3% Mild: 38.5%	Suture/ProKera
Shammas *et al.*, 2010[39]	RS	8 (16)	2-82	3:5	Severe	Suture/ProKera/AM with 24 mm Kontur bandage contact lens
Shay *et al.*, 2009[2]	Review	6 (12)	4-12	NA	Severe	Suture: 6 Cryopreserved AM: 4
Nassim *et al.*, 2021[31]	Case report	1 (2)	8 weeks	NA	Severe	NA
Elhusseiny *et al.*, 2021[40]	Case report	1 (2)	2 months	NA	Severe	Suture
Baş and Uçakhan Gündüz, 2019[41]	Case report	1 (2)	1	NA	Severe	Sutureless with symblepharon ring
Cheung *et al.*, 2016[42]	Case report	1 (2)	61	NA	Severe	Suture
Pruet *et al.*, 2014[30]	Case report	1 (2)	27	NA	Severe	Sutureless with symblepharon ring and fibrin glue
Muqit *et al.*, 2007[29]	Case report	1 (2)	10	NA	Severe	Suture

Contd...

Table 1: Contd...

Authors and publish year	Application time of symptom onset	BCVA outcome after AMT	Ocular cicatricial sequelae	Follow-up
Sharma *et al*., 2015[7]	Within 1~4 weeks	AMT group: 0.068±0.10 logMAR units Medicine group: 0.522±0.52 logMAR units	No cases in AMT group	6
Gregory, 2011[33]	3-10 days	All ≥20/30	Mild-to-moderate cicatricial sequelae	≥6 months
Shanbhag *et al*., 2020[3]	5 days	87% (48/55) of eyes ≥20/40	78% (43/55): MGD 58% (32/55): Dry eye	2.5 (1.2-3.6) years
Yang *et al*., 2020[34]	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[27]	66% within 7 days	92% in AMT group BCVA ≥20/40	17% in AMT group	2.6 years
Ahmad *et al*., 2017[35]	2-14 days	86.9% SJS >20/40	7%	NA
Agrawal and Pratap, 2015[36]	NA	NA	NA	NA
Ma *et al*., 2015[37]	NA	All ≥20/40	Formation of symblephara to be less	2-24 months
Kim *et al*., 2013[38]	NA	Mean logMAR significantly improved in adult and pediatric group	A significant improvement in adult group	NA
Hsu *et al*., 2012[8]	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 No AMT: 41.7 months
Shammas *et al*., 2010[39]	4-12 days	4 patients >20/40	5 patients	Mean 7.7 months
Shay *et al*., 2009[2]	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[31]	8 days	NA	Intermittent presence of mucus on the ocular surface	NA
Elhusseiny *et al*., 2021[40]	5 days	NA	No signs of ocular sequelae	NA
Baş and Uçakhan Gündüz, 2019[41]	3 days	NA	No signs of ocular sequelae	2 years
Cheung *et al*., 2016[42]	8 days	20/20 OD 20/25 OS	Mild symblephara/MGD	4 months
Pruet *et al*., 2014[30]	5 days	20/20 OU	Mild symblephara	2 months
Muqit *et al*., 2007[29]	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 applicated, 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.[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.[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 B20/40; however, eyelid-related complications and dry eyes remain a common problem even with the use of AM.[3] The outcome of BCVA in a majority of patients (50%–100%) can reach more than 20/40 after early AM treatment.[2,3,27,33,34,39] Evidence also reveals that delayed AMT is associated with worse BCVA and ocular surface outcome. In a retrospective cohort study from Yang *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.[34] A similar outcome was also presented in case–control studies from Gregory[33] and Hsu *et al*.[8]

Early involvement of ophthalmologists or easy-applicated 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.[34,43] Most patients were admitted to the intensive care unit (ICU) or emergency room (ER) after the initial symptom onset.[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.[34] Studies show that pediatric patients tend to have more severe ocular involvement,[34,38,44] and may benefit from earlier intervention with AMT. The study from Basu 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.[44] Therefore, an easy-applicated AMT, such as ProKera® 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.[45] 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.[39] Although ProKera® only covers the cornea and surrounding bulbar conjunctiva, leaving the rest of the conjunctiva, fornixes, and eyelid margins exposed, its advantages include easy bedside insertion without sedation and easy replacement if the membrane melts.[37] Mild and moderated SJS patients can be initially treated with ProKera®. Severe SJS/TEN patients can be initially treated with ProKera® 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.[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 cicatricial ocular sequelae, including lid margin keratinization, trichiasis, entropion, progressive symblepharon, dry eye disease (DED), corneal pannus, and PED.[28] AMT combined with corneal limbal graft, conjunctival autograft, mucous membrane graft, and lamellar keratoplasty[10,48,49] has been used in the corneal and conjunctival surface construction of chronic SJS/TEN, for indication of PED, corneal ulcer, symblepharon, and pseudopterygium.[14,28,47]

AMT can successfully reconstruct the conjunctiva and fornix, although some severe cases have failure of construction and recurrence of symblepharon.[50] In a study from Tseng *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.[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).[51] Pseudomembranous conjunctivitis with corneal epithelial sloughing can be observed in acute GvHD within the first 100 days following HSCT.[52] The common ocular manifestation of chronic oGvHD is DED or keratoconjunctivitis sicca, which may contribute to PED.[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.[52] 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® has also been used to treat severe refractory oGvHD for indications of severe dry eye, corneal PED, ulceration, and perforation.[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® 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.[55] In some severe cases, AM can seal tiny corneal perforation so that keratoplasty can be avoided.[56,57] Nevertheless, early intervention with AM in oGvHD can significantly prevent serious complications such as corneal ulceration and perforation.[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.[60,61] The ocular manifestations include severe keratoconjunctivitis sicca, recurrent epithelial erosion, nonhealing corneal ulcers, and even corneal perforation.[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.[60] In cases that are refractory to standard therapies, the use of ProKera® is beneficial in the improvement of symptoms and ocular surface staining in patients with SS.[62] Moreover, AMT can promote the healing of corneal melting and ulceration.[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.[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® 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.[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.[66-73] PUK is a group of corneal disorders that cause peripheral corneal thinning, usually associated with systemic autoimmune diseases,[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.[75] The management should start from an accurate diagnosis by ruling out bacterial, fungal, or *Acanthamoeba* infections.[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.[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.[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.[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.[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, oGvHD, 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.

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