Indications and Outcomes of Amniotic Membrane Transplantation in the Management of Acute Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis: A Case–Control Study

Maylon Hsu, MD, Anupam Jayaram, MD, Ruth Verner, BS, Amy Lin, MD, and Charles Bouchard, MD

Purpose: To evaluate the indications and outcomes of amniotic membrane transplantation (AMT) performed within the first 2 weeks of presentation in the management of patients with acute Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Methods: A retrospective chart review from January 1998 to May 2011 identified 128 SJS/TEN patients admitted to Loyola University Medical Center Burn intensive care unit. The degree of initial ocular surface inflammation was graded as mild, moderate, or severe within the first 2 weeks of admission. Patients were managed either medically or with amniotic membrane (AM). Outcomes were graded as good [best-corrected visual acuity (BCVA) >20/40], fair (BCVA 20/40 to 20/200 or with ocular surface discomfort, requiring contact lens or reconstructive surgeries), or poor (BCVA <20/200).

Results: Of the 182 eyes (91 patients) with documented inpatient eye examinations, 108 eyes (59.4%) had mild or no initial ocular involvement, 37 eyes (20.3%) had moderate, and 37 eyes (20.3%) had severe inflammation. Of the 29 patients (58 eyes) with greater than 1 month of follow-up, 17 patients (33 eyes) were treated with medical management and 13 patients (25 eyes) were treated with early AM. One of the 23 eyes with moderate or severe presentation treated with early AMT (4.3%) resulted in a poor outcome within 3 months compared with 8 of 23 eyes (34.8%) that were medically managed ($P = 0.022$).

Conclusions: We present the first case–control study of the use of AM in the management of acute SJS/TEN. Early use of AMT prevents severe vision loss in SJS/TEN patients with initial moderate or severe ocular surface inflammation.

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From the Department of Ophthalmology, Loyola University Medical Center, Maywood, IL.

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Reprints: Charles Bouchard, Loyola University Medical Center, 2160 South First Avenue, LUH–North Entrance, Suite 2601, Maywood, IL 60153 (e-mail: cboucha@lumc.edu).

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Stevens–Johnson syndrome (SJS) is a relatively rare, acute, exfoliative blistering disorder of the skin that also involves at least 2 mucous membranes sites. It is primarily an inflammatory hypersensitivity reaction initiated by several different pharmacologic agents, such as antibiotics, anticonvulsants, and nonsteroidal anti-inflammatory drugs, or less often can be in response to different types of infections.[1] Toxic epidermal necrolysis (TEN) is a more severe form of the disease that results from a necrotic reaction, involving more than 30% of the body surface and has a reported mortality of 27% to 31%.[2,3]

SJS/TEN patients are commonly referred to a burn intensive care unit (ICU) for aggressive wound and airway management, enteral nutritional support, and to manage the potential life-threatening complications. For survivors of the acute stage, long-term sequelae may include skin depigmentation, nail deformities, vulvovaginal stenosis, and ocular surface abnormailites.[4,5] The percentage of SJS/TEN patients with ocular involvement can vary from 50% to 81%.[2,3,6,7] The ocular sequelae can range from mild dry eye to severe scarring, leading to bilateral blindness.

SJS/TEN can be divided into acute and chronic disease. The acute ocular manifestations are characterized by inflammation of the entire ocular surface: cornea, bulbar, and tarsal conjunctiva and eyelid margin. This process can range from mild localized conjunctival injection to severe pseudomembranous or membranous conjunctivitis, corneal epithelial dysfunction, and eyelid margin scarring. Inflammation may persist and result in the chronic manifestations of the disease, which include symblepharon formation and forniceal shortening. In addition to the conjunctival inflammation, there may be damage of the mucin-producing goblet cells, lacrimal ducts, and meibomian glands, as well as keratinization of the ocular surface. It is the keratinization and scarring of the eyelid margins that may be the most important prognostic factors in long-term outcomes.[8] A variety of other lid margin abnormalities may also develop, including entropion, trichiasis, and punctal occlusion. Corneal stem cell deficiency with associated conjunctivalization of the ocular surface and deeper

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corneal neovascularization may result, which is difficult to manage and prone to failure with severe visual loss.[8–10]

Amniotic membrane transplantation (AMT) has been shown to be effective in ocular surface reconstruction in the chronic stages of SJS/TEN.[10–13] More recently, it has shown promise in the acute stages to prevent or reduce the cicatricial ocular surface and lid margin anormalities.[14–19] To date, there have been no published case–control studies comparing outcomes of patients treated with AMT in the acute stages of SJS/TEN. Additionally, there are no well-accepted clinical indications for AMT, although several authors have made recommendations.[14,16,17] The specific clinical indications for AMT should be based on the level of acute inflammation that can vary greatly. To more accurately assess the benefit of early AMT, we retrospectively compared SJS/TEN patients with similar levels of acute ocular inflammation who were admitted to the Loyola University Medical Center Burn ICU. We reviewed the long-term outcomes of the eyes of patients treated medically compared with those who underwent early surgical intervention with amniotic membrane (AM).

MATERIALS AND METHODS

Clinical data were collected retrospectively on 128 SJS/TEN patients admitted to the Loyola University Medical Center Burn ICU from January 1998 to May 2011. Patients were identified using department database records, a search of records with ICD-9 codes (695.13-SJS, 695.14-SJS/TEN overlap syndrome, 695.15-TEN), and a keyword search of the pathology biopsy database for full-thickness epidermal necrosis, SJS, TEN, and erythema multiforme (EM). Patients were included if both the clinical and skin biopsy diagnoses were consistent with SJS or TEN. The baseline data included patient's age, sex, ethnicity, length of ICU admission, mortality, systemic and ocular treatments, and ocular manifestations and sequelae.

Grading System for Ocular Manifestations and Outcomes

Acute ocular involvement and long-term outcomes were graded in an unmasked fashion through review of medical records. Ophthalmology inpatient clinical examination notes were graded according to the following criteria for acute disease in the first 2 weeks of daily examinations. All patients were seen by 1 of 2 cornea specialists (A.L. or C.S.B.). *Mild* ocular involvement was defined as having mild cornea punctate epithelial erosions, epithelial defects $<25\%$ of the cornea, and/or mild conjunctival injection with no membranes or pseudomembranes. *Moderate* findings included epithelial defects up to 50% of the cornea, moderate conjunctival injection, and/or moderate membranes or pseudomembranes. *Severe* findings included epithelial defects $>50\%$ of the cornea, severe conjunctival inflammation, and/or epithelial defects, and/or extensive pseudomembranes or membranes. Examples of the variety of acute ocular surface presentations are shown in Figure 1.

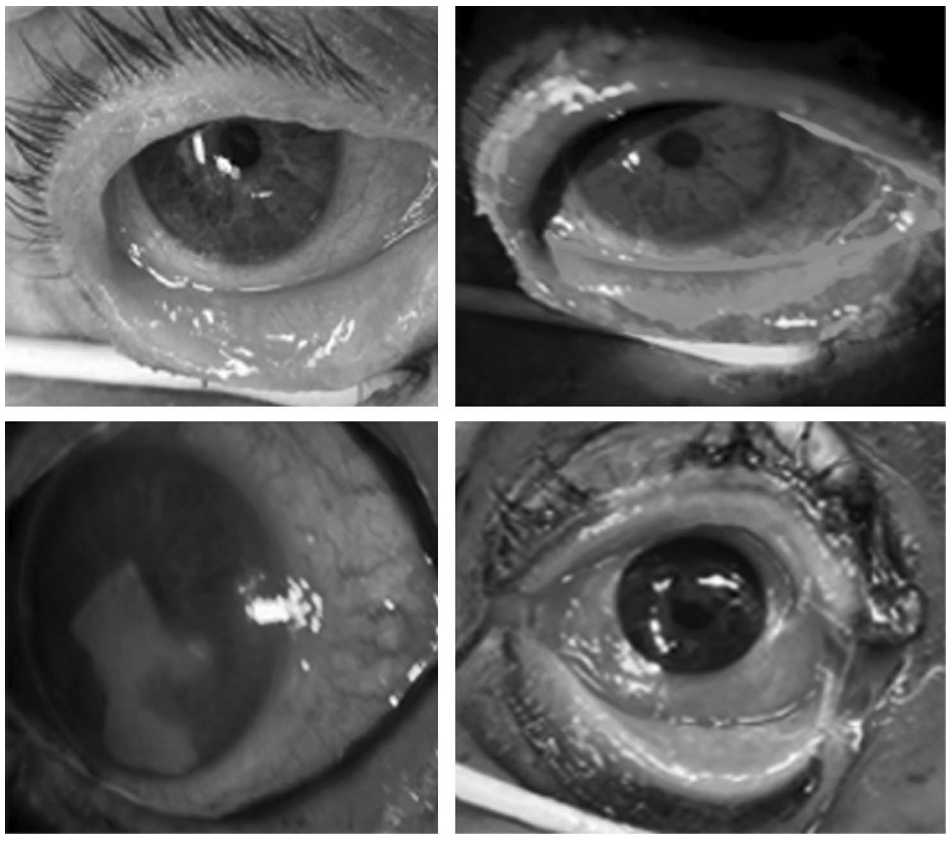

FIGURE 1. Acute ocular surface inflammatory findings: (Top left) Moderate conjunctival inflammation, with a conjunctival epithelial defect seen in the same eye with fluorescein staining (top right). (Bottom left) Moderate corneal epithelial defect with no conjunctival staining. (Bottom right) Severe conjunctival inflammation, with membrane and eyelid skin desquamation.

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Outcomes were determined retrospectively by reviewing ophthalmology outpatient examination notes. Outcomes were recorded for all patients at 1 to 3 months from disease onset to allow for equal comparison between patients. We also analyzed outcomes at the most recent recorded follow-up visit. The length of follow-up varied considerably because it included patients over a 13-year period. There was more limited follow-up for patients who received AM because it is a relatively new procedure. *Good* outcomes were defined as having best-corrected visual acuity (BCVA) >20/40 with or without mild conjunctival scarring, symblepharon, trichiasis, or mild dry eye symptoms. *Fair* outcomes were defined as BCVA 20/40 to 20/200 or ocular surface discomfort from keratinization or conjunctival scarring requiring therapeutic contact lens or reconstructive surgeries. *Poor* outcomes included BCVA <20/200 with or without ongoing complications involving the ocular surface requiring multiple interventions.

Amniotic Membrane Transplantation

Patients were included in the AM treatment group if they received either sutureless AM (ProKera; Bio-Tissue, Miami, FL) placed at the bedside or if they underwent AMT within 2 weeks of burn ICU admission. A method of AMT similar to that first described by John et al[19] was used. All procedures were performed by 1 of 2 cornea surgeons from the Loyola cornea service (A.L. or C.S.B.). There were 2 techniques used for the AMT that was performed in the operating room under general anesthesia. For most of the cases, after the upper and lower eyelashes were cut short, a 3.5-cm square of cryopreserved AM (Amniograft; Bio-Tissue), basement membrane side up, was cut in half to cover the lower and upper palpebral conjunctiva and fornix, secured with 8-0 nylon or prolene running sutures anterior to the lash line. A double-armed 6-0 prolene suture secured the AM to the tarsal conjunctiva by passing the suture through each fornix and securing it to foam bolsters on the eyelid skin. A second 3.5-cm AM graft was secured over the cornea with a 10-0 nylon running suture, approximately 1 to 2 mm from the limbus. Four 10-0 nylon interrupted sutures were used to secure the AM to the 4 quadrants of the bulbar conjunctiva. A large symblepharon ring (Jardon Eye Prosthetics, Inc, Southfield, MI) was then placed over the AM (Fig. 2) in all AMT cases except 1 patient.

In 2 patients, the method described by Rubinate et al[20] was used. This technique used three 3.5 × 3.5 cm AM grafts that were secured in a series using running 10-0 nylon sutures. The center of the middle AM was marked with a gentian violet marking pen. The AM was then secured to the upper and lower eyelid margins with running 8-0 prolene suture. A symblepharon device was then constructed from intravenous (IV) extension tubing, adjusted to approximate the AM into the fornices and still allow for complete eyelid closure. The ends of the tubing were tied together to construct a ring with a 5-0 vicryl suture (Fig. 2). In all cases with AM, daily ophthalmic examination monitored the rate of dissolution. In cases with early dissolution of AM, repeat AMT was done if there was persistent ocular inflammation.

RESULTS

Surgical and Medical Management

There were a total of 128 SJS/TEN patients who met inclusion criteria. The mortality rate was 21.9%, with an average length of ICU admission of 17.2 days. There were 14.1% of patients who received IV corticosteroids and 12.5% received intravenous immunoglobulin (IVIG) treatment (Table 1). Thirty-seven SJS/TEN patients had insufficient recorded data. Of the 91 remaining patients (182 eyes) with documented eye examinations during the first 2 weeks of admission, 108 eyes (59.4%) had mild or no ocular involvement, 37 eyes (20.3%) had moderate ocular inflammation, and 37 eyes (20.3%) had severe inflammation (Table 2). Twenty-nine patients (58 eyes) had 1 or more months of ophthalmology follow-up. Twenty patients had greater than 3 months of follow-up. The average length of follow-up after 3 months was 41.7 months for patients who did not have AMT and 13.6 months for patients treated with early AM. The remaining patients either died or were lost to follow-up. Because the LUHS Burn Unit is a tertiary referral center serving multiple states, many patients were unable to return for follow-up because of distance of travel.

Detailed analysis of ocular outcomes was conducted for the 29 patients (58 eyes) with more than 1 month of

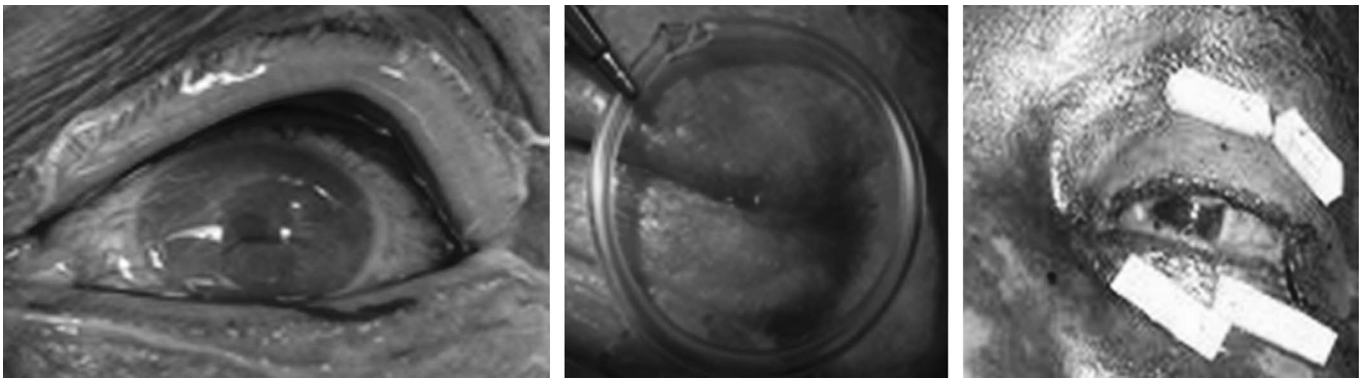

FIGURE 2. Amniotic membrane transplantation: (Left) AMT over the entire ocular surface using a symblepharon ring constructed of IV tubing (middle) to keep the membrane deep in the fornices. (Right) AMT with bolsters secured with 6-0 prolene passed through the fornices.

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TABLE 1. Baseline Data of 128 SJS/TEN Patients

	No. Patients	%
Gender		
Female	72	56.3
Male	56	43.8
Ethnicity		
Black	36	28.1
Hispanic	11	8.6
White	45	35.2
South Asian	3	2.3
Unknown	33	25.8
Age, yr		
<20	32	25.0
20–40	30	23.4
41–60	33	25.8
>60	33	25.8
Treatment		
IVIG	16	12.5
IV corticosteroids	18	14.1
Intubated	55	43.0
Death during admission	28	21.9
Average length of hospital stay	17.2 d	

ophthalmology follow-up (see Tables, Supplemental Digital Content 1, http://links.lww.com/ICO/A29). Of these patients, 17 were treated medically (33 eyes). Medical management consisted of frequent preservative-free artificial tears and ointment with daily examination and sweeping of fornices if indicated for pseudomembranes. Bandage contact lenses (Air Optix Night and Day, 8.6 mm base curve, 13.8 mm; Ciba Vision, Duluth, GA) were used for corneal epithelial defects, and in some patients, 1% prednisolone acetate (Pred Forte; Allergan, Irvine, CA) or 0.05% cyclosporine drops (Restasis; Allergan) was used 2 to 4 times daily.

The AM group included 13 patients (25 eyes) who were initially treated with either AMT or ProKera within 2 weeks of admission. Postoperatively, the majority of these patients were placed on 1% prednisolone acetate drops, 0.5% topical cyclosporine drops, and 0.5% moxifloxacin drops (Vigamox; Alcon, Fort Worth, TX) 4 times a day and 0.3% tobramycin/0.1% dexamethasone ointment (Tobradex; Alcon) at bedtime. Eleven of these patients (21 eyes) underwent AMT in the operating room under general anesthesia. In 6 patients, AMT was done on day 3 of admission and 3 had AMT done on day 5. Three eyes were initially treated with ProKera only on day 5, with subsequent AMT on days 12 and 14 for persistent inflammation ending in fair to poor outcomes. In 1 patient, ProKera was placed on admission for a large corneal epithelial defect until AMT could be done on day 3 in both eyes. Only 2 eyes required a repeat AMT on day 17 and day 12 for ongoing ocular surface inflammation after the dissolution of the first AMT.

Four eyes (2 patients) had only ProKera placed, with no further AMT. The first patient had mild initial ocular inflammation, with ProKera placed in both eyes on day 7, resulting in a good outcome at 2 months. The second patient had severe ocular inflammation but was unable to undergo AMT because of a difficult intubation requiring an emergent tracheostomy when attempted on day 3 of admission. This patient was treated with only ProKera placed on day 3 and subsequent bedside symblepharon lysis. One patient underwent AMT only, without placement of symblepharon rings.

TABLE 2. Degree of Ocular Surface Involvement in the First 2 Weeks of Admission of 182 Eyes of 91 SJS/TEN Patients

Degree	No. Eyes	%
None	38	20.9
Mild	70	38.5
Moderate	37	20.3
Severe	37	20.3

None, no ocular surface involvement; mild, mild cornea punctate epithelial erosions, epithelial defects <25% of the cornea, and/or mild conjunctival injection; moderate: epithelial defects >25% to 50% of the cornea, moderate conjunctival injection, and/or moderate pseudomembranes; severe, epithelial defects >50% or the cornea, severe conjunctival injection and/or conjunctival epithelial defects, and/or severe pseudomembranes.

Outcomes

Outcomes were compared between patients treated medically versus surgically with AM. Patients with similar levels of acute presentation were compared at 1 to 3 months and the most recent follow-up visit past 3 months (Table 3). Descriptive long-term outcomes are detailed in Table 4. There were insufficient numbers to reach statistical significance in each individual subgroup of mild, moderate, and severe acute presentation. When combining patients with either moderate or severe presentations, 1 of 23 eyes treated with early AMT (4.3%) resulted in a poor outcome within 3 months compared with 8 of 23 medically managed eyes (34.8%; $P = 0.022$, Fischer exact test; Fig. 3). When analyzing patients with either moderate or severe presentations, 1 of 23 eyes with moderate or severe presentation treated with early AMT

TABLE 3. Summary of Outcomes of SJS/TEN Patients Based on the Degree of Acute Presentation and the Use of Early AMT

Degree of Acute Presentation	Total No. Eyes	Good, No. Eyes (%)	Fair, No. Eyes (%)	Poor, No. Eyes (%)
Outcomes 1–3 mo				
No AMT				
Mild	10	10 (100)	0 (0)	0 (0)
Moderate	12	3 (25)	7 (58.3)	2 (16.7)
Severe	11	0 (0)	5 (45.5)	6 (54.6)
Early AMT				
Mild	2	2 (100)	0 (0)	0 (0)
Moderate	4	4 (100)	0 (0)	0 (0)
Severe	19	11 (57.9)	7 (36.8)	1 (5.3)
Outcomes >3 mo				
No AMT (average follow-up = 41.7 mo)				
Mild	6	5 (83.3)	1 (16.7)	0 (0)
Moderate	7	2 (28.6)	5 (71.4)	0 (0)
Severe	11	0 (0)	4 (36.4)	7 (63.6)
Early AMT (average follow-up = 13.6 mo)				
Mild	0	0 (0)	0 (0)	0 (0)
Moderate	2	2 (100)	0 (0)	0 (0)
Severe	12	7 (58.3)	4 (33.3)	1 (8.3)

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TABLE 4. Descriptive Long-term Outcomes

Case	Most Recent Follow-up (mo)	BCVA (OD; OS)	Cornea Complications and Interventions	Eyelid Complications and Interventions
Patients not treated with early AMT				
2	60	20/30; 20/20	None	Multiple electro-epilations for trichiasis, keratinization requiring SCL for comfort
3	24	20/20	Mild scar OD	Mild lid margin scarring
4	29	20/25; 20/40	Resolved bilateral epi defects, increased corneal scarring OS	Keratinization requiring SCL for comfort
5	64	CF OU	Complete keratinization OU	Multiple reconstructive surgeries for severe entropion, trichiasis, and symblepharon
6	79	20/30; 20/25(BOSP)	Progressive SCD, inferior conjunctival graft OD for epi defect	Right entropion repair
7	101	NLP OU	Conjunctival graft OD, multiple failed PKPs and KLALs for descemetocele ending in evisceration OD	Near-complete cicatrizing ankyloblepharon OS after multiple reconstructive surgeries
8	48	LP/HM	Failed PKP OS and lamellar corneal transplant OD for impending perforations	Multiple entropion and symblepharon repairs
9	5	20/100 ph 20/50; 20/40 ph 20/25	Resolved PED with inferior conjunctival flaps	Entropion OS with trichiasis
10	43	HM; 20/25	Conjunctival graft OD for impending perforation	Symblepharon repair OU, severe lid margin keratinization requiring SCL
Patients treated with AMT within the first 2 weeks of admission				
13	10	20/25; 20/40	Mild PEE	Keratinization requiring SCL for comfort, punctual cautery, meibomian gland probing
14	24	20/25 OU	None	None
15	14	20/30; 20/20	None	Mild keratinization, mild epiphora from inflammatory obstruction of punctum
17*	25	20/20 (BOSP); CF 3'	Peripheral NV OD; subtotal NV OS, SCD OS > OD	Multiple electro-epilations, symblepharon, and entropion repairs OU
18	15	20/25 OU	None	Keratinization requiring SCL
20	8	20/25; 20/20	None	Mild MGP
21†	5	20/20; 20/40	Moderate PEE OS	Symblepharon superiorly OU with forniceal foreshortening causing ptosis OS
22	4	20/20 OU	None	None

*Delayed AMT at day 14.

†No symblepharon rings used with AMT.

BOSP, Boston ocular surface prosthesis [now called PROSE (prosthetic replacement of the ocular surface ecosystem) device]; CF, counting fingers; epi, epithelial; HM, hand motion; KLAL, keratolimbal allograft; MGP, meibomian gland plugging; NLP, no light perception; NV, neovascularization; PEE, punctate epithelial erosion; ph, pinhole; PKP, penetrating keratoplasty; SCD, stem cell deficiency; SCL, soft contact lens.

(4.3%) resulted in a poor outcome within 3 months, compared with 8 of 23 (34.8%) medically managed eyes ($P = 0.022$, Fischer exact test; Fig. 3). In follow-up greater than 3 months, results were similar with poor outcomes in 7.1% of those receiving early AMT versus 38.9% of medically treated patients. However, the statistical significance was not as strong ($P = 0.053$; Fig. 4).

Mild Inflammation Group

Of 12 eyes with mild inflammation, all had good outcomes at 1 to 3 months whether treated with or without AM. Only 2 of these eyes with mild inflammation underwent ProKera placement, with good outcomes at 2 months. Only half of the patients returned for follow-up visits. Five eyes continued to have good outcomes past 3 months. In 1 non–AMT treated eye with follow-up at 24 months, vision was 20/20 but required soft contact lens management for discomfort because of increased lid margin keratinization. This was considered to be a fair outcome.

Moderate Inflammation Group

There were 16 eyes with moderate inflammation. The 4 eyes that underwent AMT resulted in good outcomes. Of the 12 eyes with moderate inflammation treated medically, 3 had good outcomes, 7 had fair outcomes, and 2 had poor outcomes. Reasons for the fair outcomes included corneal scarring decreasing vision to 20/40, lid margin keratinization requiring contact lenses, symblepharon, and fornix foreshortening preventing the use of therapeutic bandage contact lens. Two eyes of one patient resulted in poor outcomes from persistent corneal epithelial defects requiring inferior conjunctival flaps, which improved to a fair outcome at 5 months. All other patients were either lost to follow-up or had no change in recorded outcomes after 3 months.

Severe Inflammation Group

For the 30 eyes with severe ocular surface inflammation, 11 eyes were treated medically and 19 eyes were treated with AM. Six eyes of the medically treated group (54.6%)

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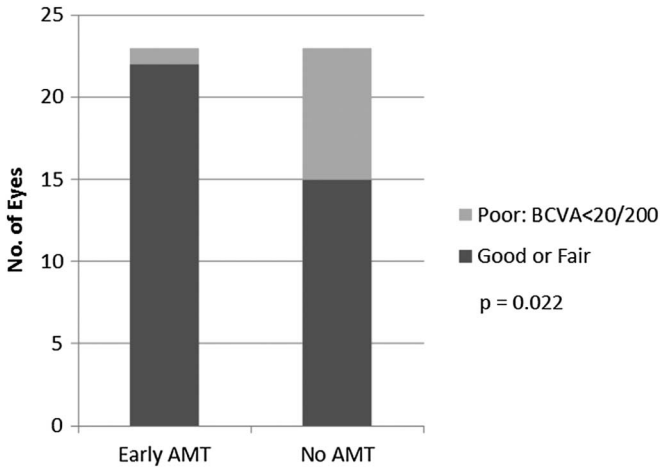

FIGURE 3. Outcome of SJS/TEN patients at 1 to 3 months with moderate or severe acute inflammation.

had poor outcomes by 3 months compared with only 1 eye (5.3%) of the AMT group. Of the eyes with severe presentation, 11 eyes (57.9%) had a good outcome in the AMT group, with no good outcomes in the medically treated group.

Of the 11 medically treated eyes with severe presentation, 1 eye with an early fair outcome developed a poor outcome with hand motion vision at 43 months, requiring a conjunctival graft for an impending perforation. Three patients resulted in poor outcomes at 3 months. These 6 eyes were found to have BCVA of counting fingers with complete corneal keratinization, no light perception after multiple cornea and limbal stem cell transplant failures ending with evisceration, a completely cicatrizing ankyloblepharon, and light perception and hand motion vision after failed corneal transplants for impending perforations (Fig. 5). In addition, all these patients had undergone numerous reconstructive ocular surface surgeries for symblepharon and entropion.

Of the 19 eyes of patients who presented with severe disease who had an early AMT, only 1 eye had a poor outcome at the 1- to 3-month follow-up visit. Ten eyes had good outcomes (Fig. 6) and 7 eyes had fair outcomes. In the follow-up visits after 3 months (average, 13.6 months), no eyes

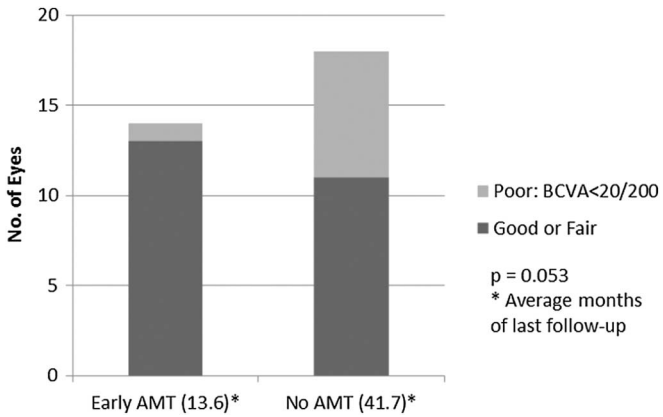

FIGURE 4. Long-term outcomes of SJS/TEN patients with moderate or severe acute inflammation.

progressed to a worse outcome category. The worst complications were in 4 patients (7 eyes) who did not have a standard AMT by day 5 as described above. Two eyes had only had ProKera placed, 3 eyes had a delayed AMT (days 12 and 14) after initial ProKera placement, and 2 eyes did not have symblepharon rings placed over an early AMT. When excluding these 7 eyes, all eyes attained BCVA ≥20/30. Two eyes had fair outcomes because of lid margin keratinization and severe dry eyes, and the remaining 10 eyes had good outcomes.

DISCUSSION

Although all SJS/TEN patients present with some mucous membrane involvement, the degree of ocular surface involvement varies from no changes to severe conjunctival, corneal, and eyelid inflammation.[2,3,6,7] Severe ocular surface damage may lead to blindness and painful cicatricial scarring. In the present study of 91 patients (182 eyes) with biopsy-proven SJS/TEN, 20.9% had no acute ocular involvement, 38.5% had mild inflammation, 20.3% had moderate, and another 20.3% presented with severe inflammation using our previously defined criteria. Our results are similar to several other retrospective studies[2,3,6,7] that used criteria initially described by Power et al,[2] defining severe inflammation as "sight threatening disease, with ongoing ocular inflammation, decreased vision, and ongoing active corneal disease at the time of discharge." Chang et al[7] and Power et al[2] retrospectively reviewed a large series of more than 200 patients that included EM patients and did not confirm SJS/TEN diagnosis in all patients with skin biopsy. The rate of any ocular involvement for SJS patients ranged from 69%[2] to 81.3%,[7] with 3.6%[7] to 27%[2] of these patients having severe ocular involvement. In the patients with TEN, ocular involvement ranged from 50%[2] to 60%,[7] with 10%[7] to 27%[2] having severe ocular involvement. Both these studies showed that EM rarely involved the ocular surface. EM is now thought to be a different entity and is no longer included in the SJS/TEN spectrum.[21] In our burn ICU, EM patients seldom require ICU admission and were not included in the study. Two other large studies reported ocular involvement in 69%[3] to 74%[6] of SJS/TEN patients, with 4%[3] to 8%[6] having severe inflammation and 8%[6] to 25%[3] with moderate inflammation.

The long-term ocular manifestation of SJS/TEN is not known. Corneal scarring has been reported in 4.7% of patients[7] and symblepharon in 17% to 19%[2] within 3 months of follow-up. Beyond 3 months, attempts to estimate ocular morbidity at many large tertiary referral centers have poor follow-up rates of 37.6%[3] to 38%.[6] Efforts are limited by the rarity of the disorder, lack of continuity of care as an acute referral center, and the high rate of mortality. These case series report severe vision loss in 2% to 8% of patients at an average of 3 to 6 years of follow-up.[2,3,6]

In the first 1 to 2 weeks of presentation, SJS/TEN patients may present with nonhealing corneal epithelial defects or ulceration, leading to a rapid loss of vision. However, some patients without any initial corneal findings may go on to develop corneal complications thought to be because of lid margin and tarsal conjunctival scarring. In analyzing patients referred for chronic SJS/TEN problems, with an average of

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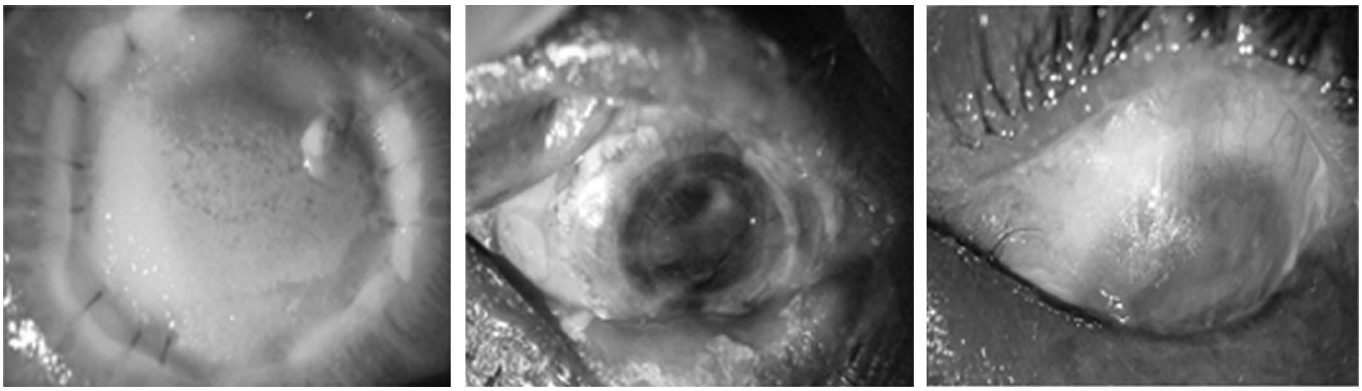

FIGURE 5. Outcomes of patients with severe ocular surface inflammation managed medically: (Left and middle) Twenty-five year old patient with multiple failed corneal and limbal stem cell transplants performed for repeated corneal ulcers and impending perforations. (Right) Seven year old patient with severe cicatricial entropion and complete keratinization of the cornea.

19 years from acute illness, Sotozono et al[10] found 53.6% of 138 eyes had vision <20/200 and 82.6% with limbal stem cell deficiency, defined by the loss of palisades of Vogt. Of 38 chronic SJS/TEN patients (76 eyes), Di Pascuale et al[8] reported a high correlation between the severity of eyelid margin and tarsal scarring to the development of blinding corneal complications when compared with symblepharon, punctal stenosis, trichiasis, aqueous tear deficiency, and floppy eyelid syndrome. The authors hypothesized that acute tarsal inflammation resulted in scarring that directly damages the corneal surface overtime from blink-induced microtrauma. In a retrospective review of 30 patients, De Rojos et al[22] found that many SJS/TEN patients develop recurrent inflammation, ocular surface failure, and mucous membrane pemphigoid, even after several years of an initially mild or moderate disease. Gueudry et al[6] found a greater likelihood of chronic ocular complications associated with the severity of acute presentation, although this was not correlated by Yip et al.[3] Furthermore, the degree of systemic involvement does not always predict the level of ocular complications either.[23]

Before the introduction of AM, acute management of SJS/TEN primarily consisted of frequent topical lubrication, topical corticosteroids, antibiotic drops, and sweeping of the fornices for symblepharon lysis and removal of membranes.[7] Araki et al[24] reported successful prevention of cicatricial outcomes with IV pulse therapy with methylprednisolone in 5 patients; however, complications from systemic immunosuppression prevents practical use in most burn ICUs. Use of systemic IVIG is also controversial,[25,26] and in 1 study, there was no benefit in SJS/TEN ocular outcomes.[3] Our burn ICU does not routinely use IV corticosteroids because the risk of infection can be life-threatening. We also do not use IVIG

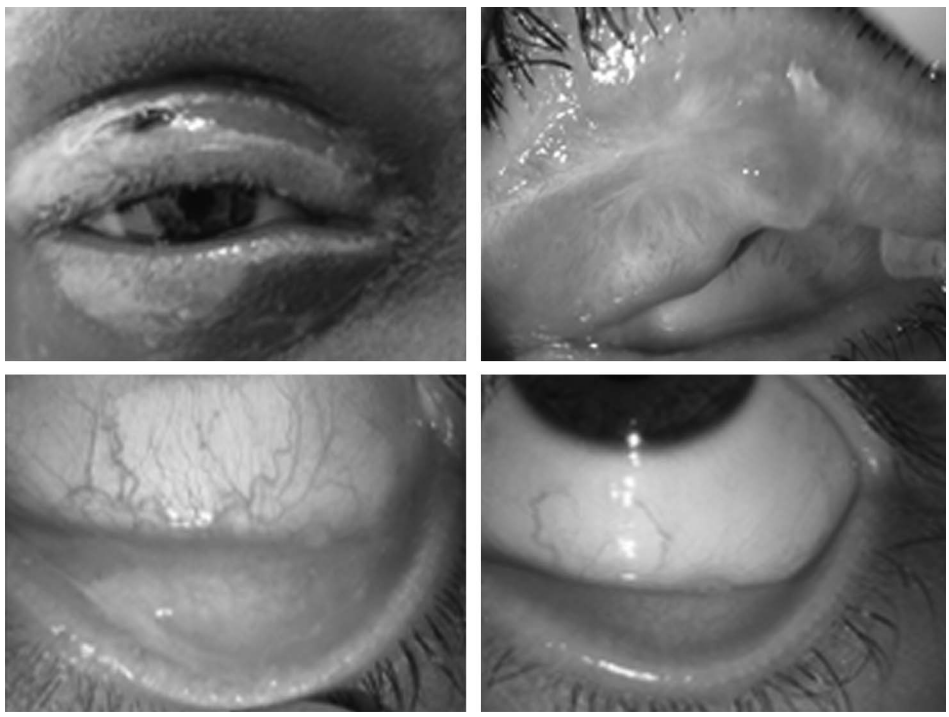

FIGURE 6. Outcomes of patients treated with early AMT. (Top left) Ten-year-old boy with quiet eyes and healing eyelids 1 week after AMT. He initially presented with acute severe ocular surface involvement shown in Figure 1 (bottom right). (Top right) Severe tarsal scarring despite multiple reconstructive surgeries and an opaque cornea with neovascularization in a 7-year-old boy who initial ProKera only and a delayed AMT on day 14. (Bottom left) Trace injection and mild lid margin scarring in a 16 year-old boy 14 months after ICU admission with initial severe inflammation. (Bottom right) 9 year-old girl with minimal lid margin scarring in quiet eyes, 5 months after initial presentation with moderate inflammation.

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because it is a costly treatment with limited evidence of its effectiveness. Because of the low percentage of patients with either IVIG or IV corticosteroids in our study, we were unable to determine the role of each with or without AMT.

Several case reports have introduced the use of AM to cover the ocular surface in the acute stages in hopes of preventing the cicatricial conjunctival changes and corneal complications.[8,15,18,19] The AM is the innermost layer of the fetal membrane composed of an avascular epithelial layer over a thick basement membrane. Use of AM has been shown to promote epithelialization and reduce inflammation and scarring, possibly through regulation of growth factors[27] or acting as a barrier to infiltrating lymphocytes,[28] although the exact mechanism is unkown.[29] Shay et al[17] reported resolution of conjunctival inflammation, no limbal stem cell deficiency, and improved vision after AMT in the acute stages in 6 pediatric patients (12 eyes) with varying degrees of lid, conjunctival, and corneal involvement.[17] Only 2 eyes showed focal symblepharon in the inferior fornix, and 2 eyes healed with fine peripheral vascularization. Shammas et al[16] reported outcomes of 4 patients (8 eyes) who underwent early AMT with a 24-mm bandage contact lens (Kontur Kontact Lens Co, Hercules, CA) placed over the AMT as an alternative to symblepharon rings, along with intense short-term topical corticosteroids. Two patients had partial AM treatment not covering the palpebral conjunctiva, resulting in 9 of the 12 eyes with greater than 20/25 vision, with limited follow-up in most patients. Most recently, Gregory[14] reported a series of 10 patients treated with early AMT for severe ocular surface inflammation with follow-up from 6 to 36 months. All patients did well with BCVA $\geq$20/30.

With promising results suggesting AMT over the entire ocular surface prevents severe ocular surface damage, our goal was to report a case–control study. Our goal was to compare outcomes of SJS/TEN patients with similar levels of ocular surface inflammation treated and not treated with early AM. Although a prospective case–control study would be most ideal, devastating blinding or lifelong cicatricial consequences in a patient, often children, precludes having 2 trial groups. We instead attempted to match controls from older medical records to more recent patients who have undergone AMT and compare patients at similar periods from disease onset. Outcomes were analyzed at the 1- to 3-month visit and also at the most recent follow-up visit.

Although we attempted to differentiate outcomes in patients with mild, moderate, and severe presentation, we had too few numbers to produce statistically meaningful results. There were definite trends that the more severe presentation, the worse the outcome, exaggerated in those patients not treated with early AMT. Continued follow-up is needed to see if initial and also multiple AMT can halt the progressive keratinization and blindness of the medically managed patients seen years after initial presentation. All the 10 patients with mild inflammation managed only medically did well, except 1 patient who later developed mild to moderate tarsal keratinization. These results suggest that in mild cases, AMT may be of little benefit.

Because our study was retrospective, reviewing documentation from over 10 years, we were limited in the specific criteria to categorize mild, moderate, and severe presentations. Conjunctival epithelial defects or staining and limbal stem cell deficiency were rarely documented, but the level of conjunctival injection, corneal staining, symblepharon, and pseudomembranes were routinely noted. Because there is subjectivity in both retrospectively reviewing notes and also performing a difficult bedside examination, an improved grading system to further study outcomes is essential. Standardization of the clinical signs of ocular surface inflammation through standard photos is needed much like that suggested by Sotozono et al[10] for chronic SJS disease. For these reasons, there may have been overlap in the moderate and severe categories. When combining eyes with moderate and severe ocular inflammation, there was a statistically significant lower incidence of poor outcomes compared with those managed medically (4.3% vs. 34.8%, $P = 0.022$) at the 1- to 3-month follow-up. This was clinically significant as well in the follow-up visits after 3 months, although there were fewer patients to provide statistically significance.

There is a broad spectrum in severity in SJS/TEN patients, which includes a subset of patients with a relentless progression of ocular surface inflammation and scarring, despite multiple interventions. In our study, by 3 months, these patients continued to have a tremendous amount of ocular morbidity, signaling a much poorer prognosis. As Gregory[14] has also demonstrated, in many patients with ongoing inflammation, multiple AMT applications may be necessary until inflammation is completely resolved, especially as AM may degrade more rapidly in these patients. Perhaps, not only early but also multiple AMT plays a critical role in these more severe patients.

Our results support the use of early AMT, within the first 3 to 5 days, over the entire ocular surface. Using only the ProKera device does not protect the palpebral conjunctiva or eyelid margin coverage where critical scarring can occur. Of the eyes treated with AMT, only 1 eye had an outcome of counting fingers vision and progressive neovascularization. This patient was only treated with ProKera and then later had a delayed AMT over the entire ocular surface at day 14. The timing of this AM may have passed the critical period for beneficial effect. From our series and that of others,[14,16] if the AM is placed more than 1 week after onset of the disease, the beneficial effects may be reduced. The one patient who did the worst in the case series reported by Shammas et al[16] had ProKera placement without AM coverage of the palpebral conjunctiva, resulting in severe symblepharon, corneal perforation, and BCVA of 20/50 in both eyes at 1 year. Gregory[14] noted that of the 3 patients with the most severe ocular sequelae, 2 patients had delayed AMT at day 10. More data are needed to better assess this factor and the role of ProKera, symblepharon rings, or large diameter Kontur contact lens in conjunction with AM over the palpebral conjunctiva. In our series, the one patient who had only AMT with no symblepharon rings developed severe forniceal foreshortening causing ptosis in 1 eye. Gregory[14] suggests that in children, ProKera may be sufficient to act as a symblepharon ring but is too small in adults to reach the fornices to prevent cicatricial changes and did not recommend ProKera without additional AMT over the entire palpebral conjunctiva.

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In conclusion, AMT in the early stages of those SJS/TEN patients who present with moderate or severe ocular inflammation can prevent destruction of the ocular surface that can lead to potential bilateral blindness occurring within 3 months after disease onset. Indications for use of AM include moderate to severe ocular surface inflammation, as defined by moderate to severe conjunctival injection or conjunctival epithelial defects, corneal epithelial defects greater than 25% of the cornea, or moderate to severe pseudomembranes or membranes. Patients with no acute ocular surface signs or mild ocular surface inflammation have a good prognosis, although further studies to monitor long-term outcomes are needed. Because of the rarity of SJS/TEN, high rate of mortality, and poor follow-up rates of many tertiary centers, we hope to expand our study to a multicenter case–control study with a standard grading system to increase the power of our study and include longer follow-up data.

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