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--Manuscript Summary--

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# Significant Impact of Cryopreserved Amniotic Membrane on Acute Ocular Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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**Running Head:** Significant Impact of Cryopreserved Amniotic Membrane on Acute SJS/TEN

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The ocular surface is covered by an epithelium encompassing an area including the cornea, the limbus and the conjunctiva bordered by the upper and lower lids. The healthy state of the ocular surface epithelium depends on a stable and protective preocular tear film when the eye is open. A stable preocular tear film is governed by sound ocular surface defense that involves effective neuroanatomic integration of compositional and hydrodynamic factors by two neural reflexes.(1) The compositional elements comprise the lacrimal gland, the meibomian gland, and the ocular surface epithelium to provide aqueous, lipid, and mucins in the tear fluid, respectively, whereas the hydrodynamic element includes effective eyelid-blinking-closure that also regulates tear evaporation, spread, and drainage.(1, 2) Dysfunction of any elements in the aforementioned neuroanatomic integration will result in ocular surface deficits that compromise the visual acuity.

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) together with chemical burns represent the worst insult to the ocular surface that may cause corneal blindness. For some patients with SJS/TEN, early blinding complications might be caused by limbal stem cell deficiency when the epithelial sloughing and stromal ulceration are wide spread. Nevertheless, a significant number of patients gradually develop corneal blindness, of which the extent is correlated with a myriad of progressive ocular cicatricial complications.(3) These cicatricial complications manifest as lid margin keratinization, scarring, symblepharon, and foreshortening of the fornix. Depending on the anatomical involvement, they can obstruct excretory ductules of the lacrimal gland, obliterate the tear reservoir, interfere with effective replenishment of tears in the meniscus, and cause inadequate blinking/closure, collectively leading to severe dry eye syndrome. Scarring of the tarsus can lead to eyelid misalignment, meibomian gland orifice metaplasia, keratinization of the mucosal surfaces, collectively leading to blink-related trauma that may cause recurrent and persistent corneal epithelial breakdown.(3,

4) To combat this potential corneal blindness at the chronic stage, results are generally not as effective despite surgical attempts are directed to correct these ocular surface deficits so as to restore ocular surface defense.(5)

It should be noted that all of the aforementioned cicatricial complications are sequelae of prolonged inflammation and ulceration. Hence, a better way of preventing corneal blindness in SJS/TEN patients is to effectively address inflammation and promote epithelial healing in the acute stage. In this regards, it should be noted that conventional treatments including lubrication, removal of pseudomembranes, mechanical lysis of symbelpharon, placement of bandage contact lenses, and administration of topical antibiotics or cycloplegic drops have been ineffective. Recent advances that show promising results are short-term systemic administration of a mega dose of steroid(6) and amniotic membrane transplantation (AMT). For the latter, the efficacy has been demonstrated in case reports,(3, 7-11), consecutive case series with short(12, 13) and long term follow up.(14, 15)

As shown in a recent report in *Ophthalmology*, one exciting new progress is made by Gregory,(16) who reported a new grading system that grades the extent of ocular surface inflammation and ulceration to guide appropriate treatments including AMT at the acute stage of SJS/TEN. This grading system utilizes fluorescein staining to assess the extent and location of epithelial defects involving cornea, conjunctiva and eye lid. It is advised that such assessment needs to be carried out daily from the first day of hospitalization regardless of the extent of the initial skin involvement. Special attention is given to the hidden areas in the fornices by applying lids retraction as well as separate, discrete sections of bulbar/ palpebral conjunctiva. According to this report, this grading system helps subdivide a total of 79 SJS/TEN patients (158 eyes) into mild (24 eyes), moderate (17 eyes), severe (28 eyes), and extremely severe cases (10 eyes.

Importantly, both mild and moderate cases that did not show corneal staining and had minimal conjunctival and lid epithelial defect maintained the visual acuity of 20/20 without chronic ocular sequelae under conventional medical treatments without AMT. However, both severe and extremely severe cases that presented with corneal epithelial defect and varying extents of conjunctiva/eyelid staining required urgent AMT and adjuvant medical treatment to achieve the visual acuity of 20/20 or > 20/25 with minimal or mild/moderate ocular sequelae. Intriguingly, placement of self-retained cryopreserved amniotic membrane facilitated immediate treatment and resulted in promising outcome if there was less extensive bulbar involvement. Gregory(16) recommend urgent AMT because the sooner AMT is performed, the more effectively it can prevent the chronic scarring sequelae. Furthermore, repetitive AMT may be necessary in severe inflamed eyes as the window of preventive treatment begins to close. It remains unclear how late during the acute stage AMT can still be effective.

The devastating cellular demise in acute SJS/TEN occurs via necrosis which is associated with intense inflammation and apoptosis mediated by cytotoxic T lymphocytes.(reviewed in(17)) The advent of AMT to achieve the aforementioned successful visual outcome stems from its anti-inflammatory and anti-scarring effects. A water-soluble matrix, HC-HA/PTX3 complex has been purified and identified from cryopreserved AM as the key component responsible for these AM's efficacies.(18-20) HC-HA/PTX3 is formed by tight association between pentraxin 3 (PTX3) and HC-HA complex, which consists of high molecular weight hyaluronic acid (HA) covalently linked to heavy chain 1 (HC1) of inter-α-trypsin inhibitor (IαI) through the catalytic action of tumor necrosis factor-stimulated gene-6. Unlike all conventional anti-inflammatory agents such as glucocorticosteroids, non-steroid anti-inflammatory agents, cyclosporine/tarcolimus, or various humanized antibodies that target at a specific action of one particular type of

inflammatory/immune cell, HC-HA/PTX3 exerts a broad anti-inflammatory action by targeting inflammatory/immune cells extending from innate to adaptive immune responses, of which the latter is involved in autoimmune dysregulation.(21) In fact, HC-HA/PTX3's anti-inflammatory action applies to activated but not resting neutrophils,(18, 22) macrophages,(22) and lymphocytes(18). HC-HA/PTX3 also exerts a direct anti-scarring effect on ocular tissue fibroblasts by suppressing TGF-β signaling, thus potentially preventing cicatricial complications.(18, 21) Besides anti-inflammatory and anti-scarring actions, HC-HA/PTX3 also uniquely maintains the phenotype of limbal niche cells so as to support the quiescence of limbal epithelial stem cells, an action crucial for regeneration.(23, 24)

These cumulative pieces of evidence strongly support that AMT should be regarded as a standard of care in the management of acute SJS/TEN to turn around the clinical outcome of an otherwise blinding disease. Consequently, we ophthalmologists should take an active role in partaking in the acute care of these patients together with other medical professionals.(25)

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