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Umbilical cord-derived mesenchymal stem cell therapy for acute Stevens-Johnson syndrome/Toxic Epidermal Necrolysis with severe ocular involvement

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Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening mucocutaneous disorders characterized by widespread epidermal necrosis and detachment. These conditions are manifestation of a type IV hypersensitivity reaction often resulting from drug exposure or infections and can lead to severe systemic and ocular complications [1]. Ocular involvement occurs in the majority of cases during the acute phase, manifesting as conjunctival inflammation, epithelial defects, and, in chronic stages, complications like trichiasis, symblepharon, and severe dry eye disease (DED) [2]. Standard management includes prompt withdrawal of the potential causative agent, systemic immunosuppression, topical anti-inflammatory therapies, and early amniotic membrane transplantation to preserve ocular surface integrity and prevent long-term sequelae [1,3]. However, there remains an unmet need for more effective and safer therapies to control inflammation during the acute phase, aiming to prevent long-term complications.

Mesenchymal stem cells possess potent immunomodulatory capabilities, mediated by the release of an array of immunoregulatory factors, suppressing both the adaptive and innate immune responses. These properties have demonstrated promising potential applications in ocular surface diseases, particularly in conditions characterized by inflammation and tissue damage [4]. Human umbilical cord-derived mesenchymal stem cells (UC-MSC) offer several advantages, such as easy procurement, high purity, abundance, and enhanced activity [5]. The use of UC-MSC circumvents the ethical concerns associated with stem cell research, minimizes immune rejection, and mitigates potential harm to donors and recipients. Allogeneic transplantation of UC-MSC elicits minimal immune responses and reduces tumorigenic risk without the use of immunosuppressants.

Recently, adipose derived-MSC therapy delivered via intralacrimal gland injection has shown promising results in improving dry eye symptoms in patients with Sjögren's syndrome, supporting the rationale for applying this delivery method in SJS/TEN-related DED [6].

Our report aims to evaluate the safety and therapeutic potential of intralacrimal gland injection of UC-MSC in patients with SJS/TEN exhibiting severe acute ocular involvement.

This pilot study was conducted at Chang Gung Memorial Hospital, Linkou Branch, Taiwan between June 1, 2021–May 31, 2022, and included patients diagnosed SJS or TEN who received compassionate treatment with UC-MSC. All UC-MSCs were manufactured under GMP/GTP-compliant conditions by BIONET Corp. (Taipei, Taiwan). As this therapy was performed under compassionate use, each case received individual authorization from the Taiwan Ministry of Health and Welfare (MOHW): Case 1 – MOHW No. 1101640608; Case 2 – MOHW No. 1101640772; Case 3 – MOHW No. 1101641387. The study adhered to the principles of the Declaration of Helsinki. Informed consent was obtained from all patients or their legal guardians.

Eligible patients met the following inclusion criteria: confirmed SJS/TEN diagnosis, involvement of >10 % total body surface area (TBSA), rapid clinical deterioration within 24 hours, and ocular involvement classified as Sotozono grade ≥2 (0–3) [7]. Exclusion criteria included pregnancy, malignancy, or immunodeficiency.

UC-MSC were derived from publicly donated human umbilical cords and processed under GMP (Good Manufacturing Practice) and GTP (Good Tissue Practice) by BIONET Corp. (Taipei, Taiwan). UC-MSCs were characterized by ≥ 95 % expression of CD105, CD44, CD29, CD90, CD73, and CD13, and ≤2 % expression of CD45, CD14, CD34, CD31, HLA-DR, and CD19. All cell batches were tested for viability and screened for infectious diseases, including HBV, HIV, HCV, CMV, Syphilis. On the day of treatment, thawed and washed cells were delivered in a temperature-controlled container and administered within 6 h.

Each patient received a single bilateral intralacrimal gland injection of 1×10^6 UC-MSCs (0.2 mL) per eye, delivered via subconjunctival route. Clinical evaluations included baseline and serial dermatologic and ophthalmologic assessments, including Schirmer's test type I (mm/5′), National Eye Instiute (NEI) corneal fluorescein staining, and best corrected visual acuity (BCVA). Adverse events were actively monitored throughout the follow-up period.

The first case was a 40-year-old male presented with bilateral red eyes, fever, and a diffuse erythematous rash with atypical target lesions involving ~10 % TBSA, without epidermal detachment. Mucosal involvement included conjunctival hyperemia and oral erosions. SJS was diagnosed, likely viral in origin, with no identifiable drug trigger.

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A

Case	Eye	Age (y)	Sex	Disease	Time from Dx to Tx (d)	Grade	Pre-injection		Post-injection 1m		Post-injection 1y	
							Schirmer (mm/5')	NEI	Schirmer (mm/5')	NEI	Schirmer (mm/5')	NEI
1	OD	40	M	SJS	45	III	4	5	8	2	10	0
	OS						15	10	17	3	23	1
2	OD	57	M	TEN	36	III	5	13	7	9	9	3
	OS						7	10	12	7	22	2
3	OD	7	M	SJS	25	III	8	4	11	3	10	1
	OS						9	7	10	4	14	2

d (days); Dx (Diagnosis); Grade (Sotozono ocular acute involvement score 0–III); Injection (intralacrimal gland injection of umbilical cord derived mesenchymal stem cell); m (months); NEI (National Eye Institute corneal fluorescein staining score 0-15); OD (right eye); OS (left eye); Schirmer (Schirmer's test type I); SJS (Stevens–Johnson syndrome); TEN (Toxic epidermal necrolysis); Tx (Treatment); y (years).

B

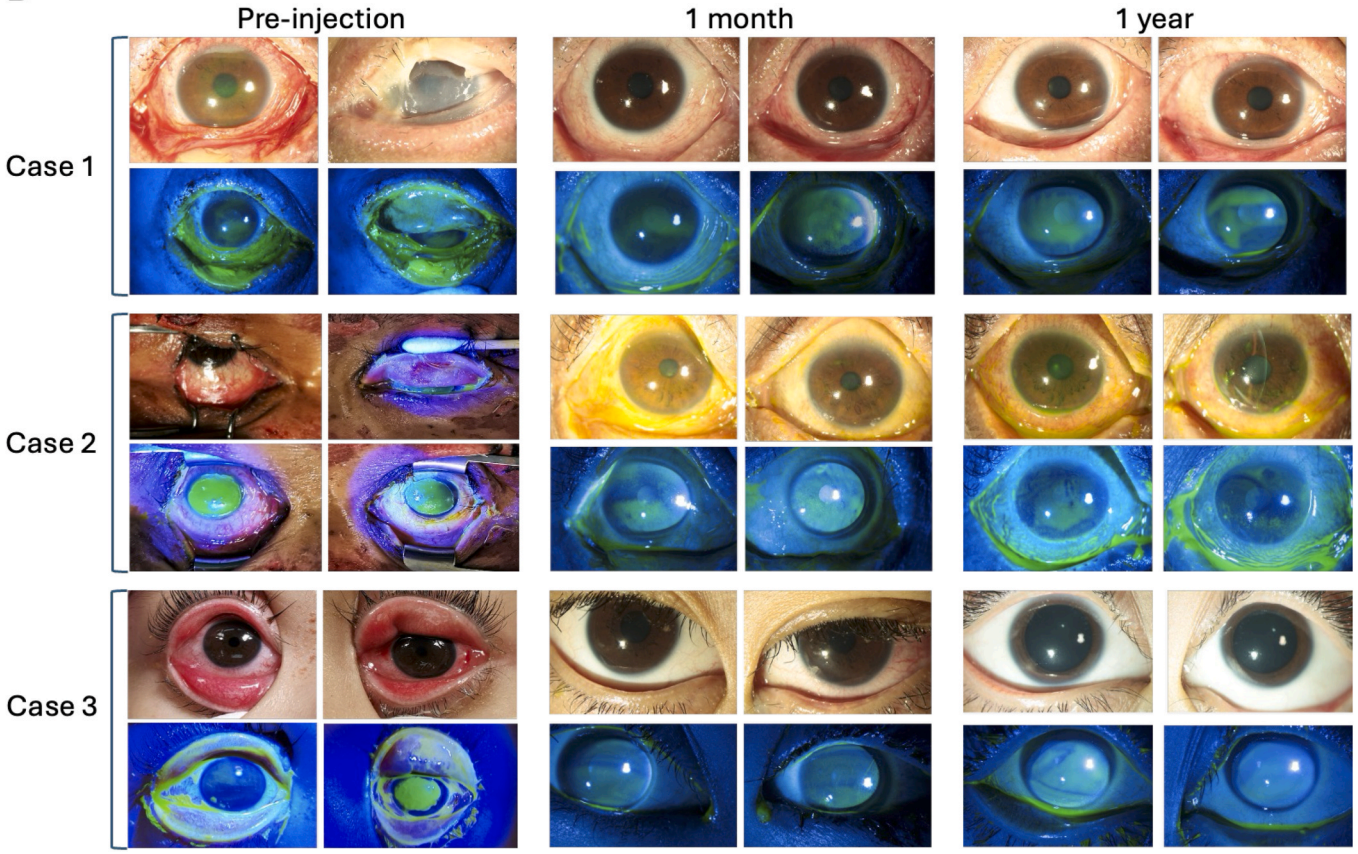


Fig. 1. A. Clinical summary and ocular surface parameters of three patients with Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) who received intralacrimal injection of umbilical cord–derived mesenchymal stem cells (UC-MSCs); **B.** Representative anterior segment photographs at baseline (pre-injection), 1-month and 1-year follow-up showing ocular surface improvement after UC-MSC therapy. For each case, images illustrate both eyes under white light and fluorescein staining with blue light filter, demonstrating improved epithelial integrity and decreased punctate keratopathy over time. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Ocular involvement was classified as Sotozono grade 3. Sutureless amniotic membrane dressing (AMD) was performed three days after diagnosis, followed by bilateral intralacrimal UC-MSC injection 45 days later. At 1 year, BCVA was preserved at 0.0 and 0.22 logMAR in the right and left eye respectively, with improvement in ocular surface parameters (Fig. 1).

The second case was a 57-year-old male with no prior comorbidities hospitalized for acute cholecystitis and underwent endoscopic retrograde cholangiopancreatography and laparoscopic cholecystectomy. Postoperatively, he developed acute respiratory distress syndrome (ARDS) and bilateral pneumonia, requiring intubation for two weeks. He received broad-spectrum antibiotics, including piperacillin-tazobactam, meropenem, and teicoplanin. Five days after starting teicoplanin, he developed a widespread bullous rash involving 50 % TBSA. TEN was diagnosed, and he was transferred to our facility. Ocular involvement was classified grade 3. He subsequently received bilateral AMD. Intralacrimal gland UC-MSC injection was administered 36 days post-diagnosis (Fig. 1). At 1 year, BCVA was preserved (0.3 and 0.4 logMAR right and left eye), with clinically significant cataracts in both eyes.

The third case was a 7-year-old male presented with high fever, skin rash, oral ulcers, and blurred vision after receiving cefixime, cefaclor, ibuprofen, and mefenamic acid for presumed tonsillitis. Examination showed bilateral conjunctivitis, oral mucosal ulceration, and maculopapular rash. Mycoplasma-induced SJS was confirmed by positive IgM serology. Ocular involvement progressed to Sotozono grade 3 and AMD was immediately performed. He received bilateral intralacrimal gland UC-MSC injection 25 days after diagnosis (Fig. 1). At 1 year, BCVA remained 0.0 logMAR in both eyes, with resolution of surface damage.

In this study, we report the safety and potential effectiveness of intralacrimal gland injection of UC-MSC in patients with SJS or TEN with ocular involvement. Over a one-year follow-up period, all three patients tolerated the procedure well, with no adverse events or complications reported following UC-MSC administration.

Our results demonstrate a significant improvement in tear production and ocular surface integrity, as evidenced by a statistically significant increase in Schirmer's test values ($p = 0.02$, ANOVA) and a marked reduction in punctate keratopathy as measured by NEI grading ($p = 0.002$, ANOVA). Importantly, BCVA was preserved in all six eyes across the three patients, indicating that the intervention may contribute to long-term visual function stability, particularly in cases at high risk of progressive ocular surface damage.

Although this study is limited by its small sample size and uncontrolled design, which restrict the ability to establish causality and generalize findings, it provides encouraging preliminary evidence supporting the safety and potential clinical benefit of UC-MSC therapy for ocular complications in SJS/TEN. The absence of a control group and randomization may introduce biases and confounding variables underscoring the need for larger, controlled trials to validate these findings.

These results suggest that intralacrimal gland administration of UC-MSCs may effectively modulate ocular surface inflammation in SJS/TEN, potentially preventing severe DED by preserving tear production and promoting epithelial repair during the acute phase.

A notable strength of this study is its focus on enhancing tear production, addressing the aqueous deficiency that is a principal contributor to chronic ocular complications in SJS/TEN. While adjunctive therapies such as AMD and systemic immunosuppressive treatments primarily target inflammation control, they may not sufficiently prevent long-term aqueous tear deficiency. In contrast, UC-MSC therapy offers a regenerative approach that not only modulates inflammation but also supports lacrimal gland function, thereby mitigating the risk of persistent DED.

To our knowledge, this is the first report of local application of UC-MSC in patients with acute SJS/TEN, highlighting its novel therapeutic potential. Promising results and the absence of complication warrant further investigation in larger, controlled trials to validate efficacy and determine optimal timing, dosing, and delivery strategies.

CRediT authorship contribution statement

Pier Luigi Surico: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Chun-Bing Chen:** Validation, Supervision, Methodology, Investigation. **Chuang-Wei Wang:** Visualization, Validation, Investigation, Data curation. **Tai Ping Lee:** Resources, Methodology. **Martin Sieber:** Resources, Methodology. **Wen-Hung Chung:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Kevin Sheng-Kai Ma:** Writing – review & editing, Visualization, Data curation. **Yueh-Ju Tsai:** Validation, Supervision, Methodology, Investigation. **Chi-Chin Sun:** Writing – review & editing, Visualization, Validation. **David Hui-Kang Ma:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Disclosures

This research received no external funding. The authors declare no conflicts of interest related to this study.

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