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LETTER TO THE EDITOR

Retrospective evaluation of a TEN/SJS series managed with a new treatment protocol

Dear Editor,

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening diseases without standardized treatment. The mortality rate ranges from 20% to 50%, and can reach up to 90%, based on the severity index SCORTEN.[1] Albeit critical, no active systemic therapeutic regimen with unequivocal benefit exists as of yet; most included cyclosporine A (CyA), immunoglobulins (IVIG) or systemic glucocorticosteroids (GCS).[2] Anti-TNF therapy has been described as beneficial in some reports,[3–5] and a randomized controlled trial was discontinued prematurely because of death excess in the thalidomide treatment group.[6] In the EuroSCAR cohort study, administration of IVIG resulted in a mortality rate of 34% (IVIG alone) and 18% (IVIG and corticosteroids).[7] However, there is no reliable consensus on the benefits or lack of benefit of any systemic treatment or combinations thereof.[8–10] Here, we report a reduction of patient mortality using a standardized triple therapy (starting 3 mg/kg CyA + 1–2 g IVIG over 3–5 days + 1 mg/kg GCS) along with an early intervention standard intensive care protocol (CPG) (Figure 1). The retrospective analysis included a total of 96 patients, 52 (54.2%) were diagnosed with SJS, 24 (25.0%) had TEN and 20 (20.8%) had SJS/TEN (Table 1). We further report an incidence of 0.36–3.53 per million TEN cases per year in Qatar, the highest reported incidence of TEN worldwide published yet. The most common causative drugs were ibuprofen (17%), Augmentin (14%), paracetamol (14%) and allopurinol (10%). Among all 96 patients, 57 (59.4%) patients had monotherapy or none, 15 (15.6%) had double therapy and 24 (25.0%) patients received triple therapy. SCORTEN was categorized into two groups: 0–2 ($n = 76$; 80.9%) and +3 score points ($n = 18$; 19.1%). Overall mortality was estimated at 8.4% ($n = 8$). The SCORTEN was significantly associated with mortality (Fisher's exact test p-value < 0.001). Simple logistic regression estimated an unadjusted mortality odds ratio of 47.73 (95% CI 5.35–425.93; p-value < 0.001) with a SCORTEN of 3+ versus 0–2. Although univariable analysis (Fisher's Exact test) did not show that triple therapy together with CPG is associated with reduced mortality (p-value > 0.999), simple logistic regression estimated an unadjusted odds ratio for mortality of 0.99 (95% CI 0.19–5.24; p-value = 0.986) for those with triple therapy and standardized care protocol. Among TEN patients, mortality dropped from 67% (2 deaths/3 patients) in 2018 to 0% (0 death/3 patients) in 2021. Among SJS/TEN patients, mortality dropped from 25% (1 death/4 patients) in 2018 to 0% (0 death/1 patients) in 2021. After introducing triple therapy in 2018, there was a 22% drop in mortality by 2021 overall, specifically a 9%, 67% and 25% drop in mortality among SJS, TEN and SJS/TEN patients, respectively. Next to the drop in mortality, patients showed fewer side effects (e.g. infections). Wounds and pulmonary infections were reported among 56 patients (58.9%), with a similar distribution among SJS, SJS/TEN and TEN (p-value = 0.939). Eye complications were reported in 44 patients, also showing no significant difference between treatment groups (p-value = 0.089). Following the introduction of triple therapy, a decrease in complications was reported, albeit statistically non-significant. This is a new protocol compared to published literature and demonstrates thus far one of the highest reductions in mortality for SJS/TEN in a comparable cohort. Limitations of the study include the open-label and non-randomized nature of the study preventing to unequivocally conclude the triple therapy regimen efficacy in SJS/TEN. Furthermore, despite histopathological confirmation and board-certified dermatologist diagnosis of SJS/TEN, the possibility of misdiagnosis cannot be completely ruled out. Other limitations include the low number of patients and improved supportive care which could contribute to better survival outcomes. In the future, large-scale prospective randomized studies are urgently needed to validate the benefit of the new triple therapy on mortality/morbidity for patients with SJS/TEN.

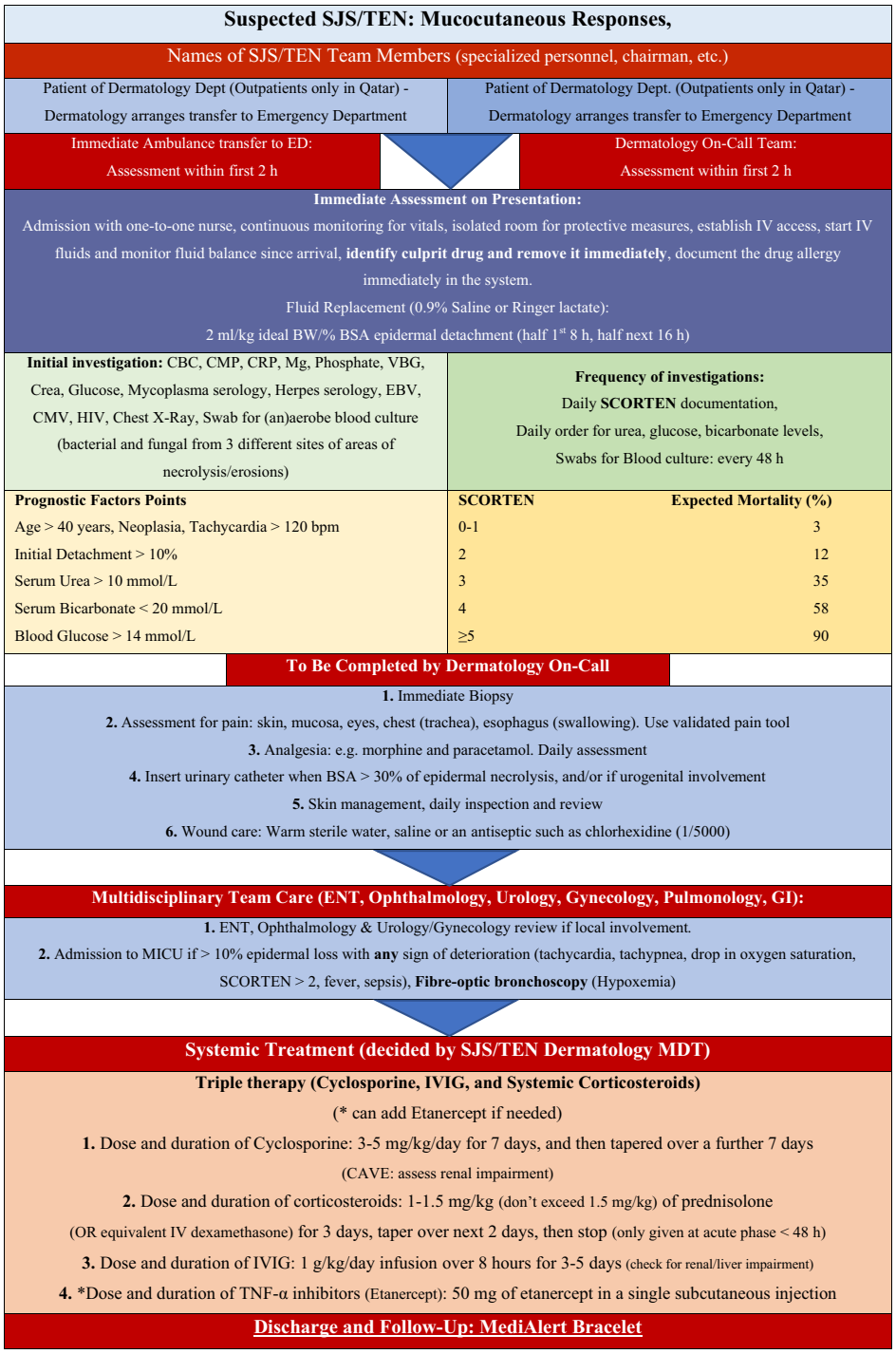

FIGURE 1 Clinical practice guidelines (CPG) for the diagnosis and management of SJS/EN in the State of Qatar. The CPG applies to all adult patients presenting with SJS, TEN or with SJS/TEN. Immediate assessment on presentation includes initial investigation: CBC, CMP, CRP, magnesium, phosphate, VBG, creatinine, glucose, mycoplasma serology, herpes serology, EBV, CMV, HIV, chest x-ray, swab for culture (bacterial and fungal from three different sites of areas of necrolysis/erosions). Triple therapy (cyclosporine, IVIG and systemic corticosteroids): Dose and duration of cyclosporine: 3–5 mg/kg/day for 7 days, and then tapered over a further 7 days (make sure there is no renal impairment). Dose and duration of corticosteroids: 1–1.5 mg/kg (not to be exceeded) of prednisolone (or equivalent IV dexamethasone) for 3 days, tapered in the next 2 days, then stop (only given at acute phase <48 h; pay attention to risk of sepsis). Dose and duration of IVIG: 1 g/kg/day infusion over 8 h for 3–5 days (make sure there is no renal/liver impairment). Dose and duration of TNF-alpha inhibitors (etanercept): 50 mg of etanercept was administered in a single subcutaneous injection. TNF-alpha inhibitors were used as monotherapy, second-line therapy or combination therapy.

TABLE 1 Mortality rates of cases of SJS, SJS/TEN and TEN diagnosed from 2015 to 2021.

		Death/case (% mortality)			
		SJS	TEN	SJS/TEN	Combined
Year of onset	2015	0/6; 0%	0/1; 0%	0/2; 0%	0/9; 0%
	2016	0/1; 0%	0/3; 0%	1/4; 25%	1/8; 13%
	2017	0/11; 0%	1/1; 100%	0/2; 0%	1/14; 7%
	2018	1/11; 9%	2/3; 67%	1/4; 25%	4/18; 22%
	2019	0/16; 0%	1/4; 25%	0/1; 0%	1/21; 5%
	2020	0/4; 0%	0/7; 0%	1/6; 17%	1/17; 6%
	2021	0/3; 0%	0/5; 0%	0/1; 0%	0/9; 0%

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CONFLICT OF INTEREST STATEMENT

M.S. is a consultant for Pfizer, Janssen, Eli-Lilly, Novartis, Abbvie, UCB, Celgene, Galderma, Leo, MenloTx, Sanofi and Regeneron. Grants by Pfizer, Novartis, Leo, Galderma and a speaker for Pfizer, Janssen, Eli-Lilly, Novartis, Abbvie, UCB, Celgene, Galderma, Leo, MenloTx, Sanofi, Union and Regeneron. S.A.K., J.B. and F.J. are investigators in a Novartis-sponsored clinical study. J.B. holds shares of Immatics N.V. and BioNTech. All other authors declare that they do not have any conflict of interest within the scope of the submitted work.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

This study was conducted in accordance with the Declaration of Helsinki and was performed according to national laws and approved by the relevant Human Ethics Review Committee, approval #MRC-01-21-763.

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