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Lower-than-predicted mortality in a predominantly HIV-infected population with epidermal necrolysis regardless of HIV status: implications and challenges for interventional studies

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TO THE EDITOR:

Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), collectively referred to as epidermal necrolysis (EN), form a spectrum of the same life-threatening disease. In SJS, there is <10% of body surface area with epidermal detachment, whereas in TEN, there is >30%. SJS/TEN overlap lies between these 2 extremes. Currently, there is no consensus on the management of EN except for supportive care. The few randomized controlled studies have not been conclusive, and current practices still rely on small cohort studies.[1–3] Apart from rarity, reasons for this include variations in the demographics, regional differences in prescribing patterns and drug use, inconsistent case definitions, differing management protocols, and inconsistent definition of treatment outcomes. Roujeau et al[4] recently suggested that a concerted global effort is needed to collect quality data on the impact of cyclosporine A (CsA) in halting disease progression and reducing EN-associated mortality. This follows recent studies that provided substantive evidence that CsA may reduce mortality in EN.[5]

In the proposed multicenter study, data from different populations managed using different protocols will need to be pooled and analyzed together. This will require harmonization of treatment protocols and management of the abovementioned inconsistencies. The severity-of-illness score for toxic epidermal necrolysis (SCORTEN) is currently the most widely used tool to predict mortality rates, although its accuracy has been questioned in certain settings.[1] One particular challenge of assessing baseline EN-associated mortality is the heterogeneity of standard of care therapies, particularly the use of oral corticosteroids and

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intravenous immunoglobulins. There is a paucity of population-specific mortality rates from settings using supportive care exclusively. We believe that baseline population—specific mortality rates will be critical to determine sample sizes required to show a benefit or deleterious effect of any intervention and the number needed to treat (NNT) to save one life. This point is well illustrated by the retrospective analysis of our baseline EN-mortality data from our HIV tuberculosis endemic setting.

In our study, we set out to determine the mortality rate in our predominantly HIV-infected cohort of patients with EN managed by the dermatology service at Groote Schuur Hospital, a tertiary hospital in Cape Town, South Africa. We reviewed clinical records of all cases seen between January 2001 and December 2015. The management of EN throughout the study period was exclusively supportive. This included oral fluid resuscitation, enteral nutritional support, daily baths with antiseptic solution, and sterile nonadherent dressings. No physical debridement of necrotic tissue was performed. Intravenous lines were only used when intravenous antibiotics or urgent resuscitation was necessary and indwelling catheters were generally avoided. No prophylactic antibiotics, systemic steroids, intravenous immunoglobulin, cyclosporine, or other specific therapeutic medications were administered to any of the patients. Anticoagulation was only administered to patients who were bed-bound for more than 7 days.

These findings are summarized in Table I. The study population was disproportionately female, < 40 years old, and none of the patients had a recent malignancy. Seventy-eight percent of our patients were HIV infected with low CD4 counts. We used the available SCORTEN parameters in our records (age, heart rate, serum urea, and affected body surface area) to calculate expected mortality. Our SCORTEN-predicted versus actual observed mortality was: overall cohort 6.9% versus 3.3%; HIV-infected cases only 7.0% versus 4.2%; and HIV uninfected cases only 9.5% versus 0%. SCORTEN overestimates mortality in our cohort regardless of HIV status. This may be attributable to a number of factors including:

1. Demographics of the study population such as age. Our population was relatively younger, median age <40 years compared with other large studies. Forty is considered the cutoff for the age-related increase in EN mortality.[1,6]
2. Timing of SCORTEN. The optimum time to perform the score is unclear and suggestions vary from day 0, 3, or 5 or performing the score on multiple days to include peak severity of the disease. The interval between disease onset and hospitalization may also impact the score.[6]
3. In retrospective EN studies with missing data like ours, SCORTEN is less accurate and an auxiliary score to improve it has been suggested.[7]
4. Comorbidities, including tuberculosis, are well-established predictors of mortality in EN, but the impact of HIV in EN-associated mortality has not been established.[1,8]
5. Pharmacological properties of a drug like its half-life and nephrotoxicity are known to impact on the acute clinical presentation of EN. This has been

established for some drugs but is currently unclear for the common offending drugs, nevirapine, or antituberculosis drugs in our population.[1,6]

6. Exclusively supportive care without use of immunosuppressants may also be protective.

In a recent study discussing the benefits of CsA in EN, Gonzalez-Herrada et al[5] assume an EN-mortality rate of 30% nd an NNT of 6 to save one life. In contrast, using our mortality figures, the NNT is 36 patients. This has a significant impact when considering a study assessing utility of CsA in reducing mortality in our population. Furthermore, if the benefit of CsA was confirmed, the low baseline EN-mortality and consequent high NNT might mean that cost-efficacy may prevent use of a relatively expensive drug in a resource-limited setting.

HIV infection is associated with a higher incidence of EN, and HIV-infected persons are therefore likely to form a significant portion of the global cohort proposed by Roujeau et al.[1,4] In addition to population-specific drug efficacy and mortality outcomes, the other important consideration in our setting will be drug toxicities. CsA can cause acute renal injury (AKI). AKI and chronic renal disease are independent predictors of mortality in EN.[1,9] HIV-associated nephropathy, which can be rapidly progressive and present as end-stage renal failure, has an estimated prevalence as high as 83% in sub-Saharan Africa.[10] Many drugs commonly used in HIV cause AKI. Examples include tenofovir, a first-line drug in most of the current antiretroviral regimens, and aminoglycosides.[10] The latter are used as second-line drugs in the treatment of drug-resistant tuberculosis and as alternatives in EN caused by first-line antituberculosis drugs, both common scenarios in HIV-infected populations.[11] Concomitant use of these drugs with CsA is likely to worsen the current toxicity profile of CsA in EN, and potentially the outcomes of any study in this population. Systemic steroids are also used in the management of EN in many centers.[1] Although this was for longer periods than is applicable in EN, the use of systemic steroids in HIV has been associated with an increased risk of HIV-related cancers and opportunistic infections.[12] Recent studies suggest that TNF-α blockers improve outcomes in EN.[3] A major side effect of these drugs is activation of latent tuberculosis. It is well established that HIV-infected persons have a much higher risk of getting infected with tuberculosis and reactivation of latent tuberculosis. Tuberculosis is a major cause of mortality in this population.[11]

Up to now, EN studies that have shown increased or reduced mortality rates associated with any immunomodulator have been based on single digit differences between SCORTEN predicted and observed mortalities.[2,3,5] Thus, in HIV-infected persons, the majority of whom are managed in resource-limited settings, the impact of immunomodulation on the patients themselves and overall mortality rates have to be carefully considered in the study design. Despite these challenges, we strongly believe that HIV-infected patients should be included in any international collaborative studies on EN so that the full spectrum of the disease is researched.

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Clinical Implications

- Although epidermal necrolysis (EN) is more common in HIV, we show lower-than-expected mortality rate in a predominantly HIV-infected population regardless of HIV status. Immunomodulators are being trialed to improve EN outcomes, but in HIV unique challenges exist. These must be considered when designing interventional studies for EN.

TABLE I.

Baseline characteristics and outcomes of 184 patients with epidermal necrolysis seen between 2001 and 2015 at Groote Schuur Hospital stratified by HIV infection

Characteristic	Total (n = 184)	HIV-infected (n = 142; 77.5%)	HIV-uninfected (n = 42; 22.8%)	*P* value
Age in years, median (IQR)	39.5 (34–47)	39 (35–44)	42 (32–57)	.23
Age ≤ 40 y, n (%)	102 (55.4)	85 (59.9)	17 (40.5)	.03
Gender, female—n (%)	128 (69.6)	104 (73.2)	24 (57.1)	.05
Race, self-reported African descent—n (%)	130 (70.7)	113 (79.6)	17 (40.5)	<.01
HIV infected				
CD4 count (cells/mm^3) on admission, median (IQR)	185 (97–264)	185 (97–264)	Not applicable	
On antiretroviral therapy, n (%)	90/142 (63.4)	90 (63.4)	Not applicable	
On tenofovir, n (%)	37/90 (41.1)	37/90 (41.1)	Not applicable	
Body surface area affected, n (%)				
<10%	114 (62.0)	92 (64.8)	22 (52.4)	.08
10% to 30%	42 (22.8)	27 (19.0)	15 (35.7)	
>30%	28 (15.2)	23 (16.2)	5 (11.9)	
Elevated blood pressure on admission (systolic/diastolic >140/90 mm Hg), n (%)	7 (3.8)	3 (2.1)	4 (9.5)	.03
Known with hypertension, n (%)	15/184 (8.2)	4 (2.8)	11 (26.2)	<.01
On antihypertensives, n (%)	14/15 (93.3)	4 (2.8)	10 (23.8)	<.01
Renal impairment on admission, n (%)	31/184 (16.8)	25 (17.6)	6 (14.3)	.90
Urea ≥10 mmol/L, n (%)	10/31 (32.3)	7/25 (28.0)	3/6 (50.0)	.30
Creatinine >120 mmol/L), n (%)	9/31 (29.0)	6/25 (24.0)	3/6 (50.0)	.21
SCORTEN*				
0–1	128/184 (69.6)	102 (71.8)	26 (61.9)	.42
2	48/184 (26.1)	34 (23.9)	14 (33.3)	
3	8/184 (4.3)	6 (4.2)	2 (4.8)	
Expected mortality	13/184 (6.9)	10 (7.04)	4 (9.5)	.59
Admission outcome, n (%)				.51
Deceased	6/184 (3.3)	6 (4.2)	0	
Discharged alive	171/184 (92.9)	131 (92.3)	40 (95.2)	
Lost to follow-up	7/184 (3.8)	5 (3.5)	2 (4.8)	

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IQR, Interquartile range; *SCORTEN*, severity-of-illness score for toxic epidermal necrolysis.

[*] Data were not available for glucose and serum bicarbonate for any patient. Expected mortality for the cohort was calculated using the data from the SCORTEN parameters that were available.