Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis: Update In Therapeutic Approach

Dr Oh Choon Chiat
Associate Consultant
Department of Dermatology
Singapore General Hospital
WARNING

The following slides contain graphic images that some viewers may find disturbing.
Adverse drug reactions

• Exanthematous

• Fixed drug eruption

• Drug-induced hypersensitivity syndrome (DIHS)/ Drug-related eosinophilia with systemic symptoms (DRESS)

• Epidermal necrolysis: Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)
What type of drug reaction is this?

a. Drug-Induced Hypersensitivity Reaction
b. Exanthematous
c. Fixed Drug Eruption
d. Stevens-Johnson Syndrome
e. Vasculitis
Day 0 = when rash first appeared
Exanthematous eruptions

• Most common of all cutaneous drug eruptions (~90%)
• Limited to the skin
• Lesions initially appear on the trunk and spread centrifugally to the extremities in a symmetric fashion
• Erythematous macules and infiltrated papules
• Pruritus and mild fever may be present
• Skin lesions usually appear more than 2 days after the drug has been started, mainly around day 8-11, and occasionally persists several days after having stopped the drug
What’s the likely diagnosis?

1. Bullous pemphigoid
2. Erythema migrans
3. Fixed drug eruption
4. Spider bite
5. Vasculitis
-21  -14  -10  -7  -3  Day 0  +3  +7

Albuterol
Morphine
Hydromorphone
Lisinopril
Ceftriaxone
Coumadin
Heparin

Day 0 = when rash first appeared
Fixed Drug Eruption

• Adverse drug reaction characterized by the formation of a solitary erythematous patch or plaque that will recur at the same site with re-exposure to the drug

• This distinguishing feature is why it’s called “fixed”

• Commonly involved drugs include: phenolphthalein (laxatives) /barbiturates / tetracyclines/ metronidazole/ sulfonamides/ NSAIDs
This patient had a FDE to acetaminophen

This patient had a FDE to doxycycline
Erythematous erosions

Erythematous macules
What is the next best step in management?

1. Consult dermatology

2. Discontinue all non-life-sustaining medications

3. Request a tissue biopsy to confirm suspected diagnosis

4. Consider transfer to burn unit

5. All of the above
HOW TO BREAK BAD NEWS TO A DERMATOLOGIST
Day 0 = when rash first appeared
Dusky appearance

Mucous membrane involvement
Extensive sloughing

Tender/painful skin
Figure 1 Pictural representation of SJS, SJS-TEN overlap and TEN showing the surface of epidermal detachment (Adapted from Fig 21.9 Bologna and Bastuji-Garin S. et al. Arch Derm 129: 92, 1993)
<table>
<thead>
<tr>
<th>Clinical entity</th>
<th>SJS</th>
<th>SJS-TEN overlap</th>
<th>TEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary lesions</td>
<td>Dusky red lesions</td>
<td>Dusky red lesions</td>
<td>Poorly delineated</td>
</tr>
<tr>
<td></td>
<td>Flat atypical targets</td>
<td>Flat atypical targets</td>
<td>erythematous plaques</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Epidermal detachment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dusky red lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Flat atypical targets</td>
</tr>
<tr>
<td>Distribution</td>
<td>Isolated lesions</td>
<td>Isolated lesions</td>
<td>Isolated lesions (rare)</td>
</tr>
<tr>
<td></td>
<td>Confluence (+) on</td>
<td>Confluence (+++) on</td>
<td>Confluence (+++) on face,</td>
</tr>
<tr>
<td></td>
<td>face and trunk</td>
<td>face and trunk</td>
<td>trunk, and elsewhere</td>
</tr>
<tr>
<td>Mucosal involvement</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>Usually</td>
<td>Always</td>
<td>Always</td>
</tr>
<tr>
<td>Detachment (% body surface area)</td>
<td>&lt;10</td>
<td>10-30</td>
<td>&gt;30</td>
</tr>
</tbody>
</table>
Fig 1. Toxic epidermal necrosis. Patient with denudation of the epidermis in sheets resembling wet cigar paper. Note the widespread involvement of the trunk.

Fig 2. Toxic epidermal necrosis. Patient with denudation of the epidermis in sheets resembling wet cigar paper. Note the widespread involvement of the right upper extremity.

Fig 3. Toxic epidermal necrosis. Patient with denudation of the epidermis in sheets resembling wet cigar paper. Note the widespread involvement of the bilateral lower extremities.

Fig 4. Toxic epidermal necrosis. Extensive blisters and erosions involving >50% of the body surface area.

Fig 5. Toxic epidermal necrosis. Extensive blisters and erosions.

Fig 6. Toxic epidermal necrosis. Intense bullae formation that is positive for the Nikolsky and Asboe-Hansen signs.
### Table 2 SCORTEN severity-of-illness score

<table>
<thead>
<tr>
<th>SCORTEN Parameter</th>
<th>Individual score</th>
<th>SCORTEN (sum of individual scores)</th>
<th>Predicted mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 40 years</td>
<td>Yes = 1, No = 0</td>
<td>0-1</td>
<td>3.2</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Yes = 1, No = 0</td>
<td>2</td>
<td>12.1</td>
</tr>
<tr>
<td>Tachycardia (&gt;120/min)</td>
<td>Yes = 1, No = 0</td>
<td>3</td>
<td>35.8</td>
</tr>
<tr>
<td>Initial surface of epidermal</td>
<td>Yes = 1, No = 0</td>
<td>4</td>
<td>58.3</td>
</tr>
<tr>
<td>detachment &gt;10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum urea &gt;10 mmol/l</td>
<td>Yes = 1, No = 0</td>
<td>&gt;5</td>
<td>90</td>
</tr>
<tr>
<td>Serum glucose &gt;14 mmol/l</td>
<td>Yes = 1, No = 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicarbonate &gt;20 mmol/l</td>
<td>Yes = 1, No = 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organ/system</td>
<td>Complication</td>
<td>Management</td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Integumentary system</td>
<td>Dyspigmentation, eruptive melanocytic nevi, onycholysis, onychodystrophy, loss of fingernails, and hair thinning</td>
<td>Prompt referral to specialized unit. Removal of devitalized epidermis. Cover with nonadherent dressing. Avoid frequent dressing change which may impede re-epithelization. Skin coverage treatment: biologic, biosynthetic, silver, or antibiotic-impregnated dressing. Active infection surveillance via skin lesion culture every 48 hours; prophylactic antibiotic use not indicated. Environmental temperature control. Aseptic handling and sterile field creation. Venous peripheral access away from the affected areas.</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Chronic bronchitis, bronchiectasis, bronchiolitis obliterans, bronchiolitis obliterans organizing pneumonia, and respiratory tract obstruction</td>
<td>Careful monitoring of respiratory function. Supplemental oxygen as necessary. Initiate intubation and mechanical ventilation if trachea and bronchi are involved. Aerosols, nebulized saline, bronchodilators, bronchial aspiration, and physical therapy.</td>
<td></td>
</tr>
<tr>
<td>Genitourinary system</td>
<td>Dyspareunia, adhesions, introtal stenosis, erosive vulvovaginitis or balanitis, urethral erosions, and genitourinary strictures</td>
<td>Urology consultation. Regular manual lysis to minimize adhesions. Foley catheter to maintain patency of urinary tract.</td>
<td></td>
</tr>
</tbody>
</table>
**Table I.** Drugs at risk for causing toxic epidermal necrolysis*

Nevirapine  
Lamotrigine  
Carbamazepine  
Phenytoin  
Phenobarbital  
Cotrimoxazole and other antiinfective sulfonamides  
Sulfasalazine  
Allopurinol  
Oxicam nonsteroidal antiinflammatory drugs  
Aminopenicillins  
Cephalosporins  
Quinolones

*Data from Roujeau et al.\textsuperscript{28} and Mockenhaupt et al.\textsuperscript{58}

**Table II.** Drugs that are commonly associated with a risk of Stevens–Johnson syndrome/toxic epidermal necrolysis based on the algorithm for drug causality for epidermal necrolysis*

<table>
<thead>
<tr>
<th>Allopurinol</th>
<th>Minocycline</th>
<th>Phenytoin</th>
<th>Carbamazepine\textsuperscript{†}</th>
<th>Nevirapine</th>
<th>Sulfasalazine</th>
<th>Fluoroquinolones</th>
<th>Nonsteroidal antiinflammatory</th>
<th>Trimethoprim-sulfamethoxazole</th>
</tr>
</thead>
</table>

*Data from Dobrosavlievic et al.\textsuperscript{50} Mockenhaupt et al.\textsuperscript{56} Guillaume et al.\textsuperscript{59} and Sassolas et al.\textsuperscript{50}

\textsuperscript{†}Human leukocyte antigen-B*1502 pharmacogenetic screening recommended for patients of Han Chinese/Southeast Asian ancestry.
# Drug allergy

<table>
<thead>
<tr>
<th>Drug</th>
<th>HLA allele</th>
<th>Ethnicity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>B*5801</td>
<td>Han Chinese, Thai, Koreans, Japanese, European</td>
<td>[19–24]</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>B*1502</td>
<td>Han Chinese, Indians, Europeans, Thai</td>
<td>[6,7,8,10,28]</td>
</tr>
<tr>
<td></td>
<td>B*1511</td>
<td>Korean, Japanese</td>
<td>[9]</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>A*3101</td>
<td>Han Chinese, Japanese, Europeans</td>
<td>[12–14]</td>
</tr>
<tr>
<td>Methazolamide</td>
<td>HLA-B<em>5901, HLA-CW</em>0102</td>
<td>Korean, Japanese</td>
<td>[29]</td>
</tr>
<tr>
<td>Oxicam</td>
<td>B<em>73; A</em>2, B*12</td>
<td>European</td>
<td>[23,30]</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>B*1502</td>
<td>Han Chinese</td>
<td>[17]</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>B*1502</td>
<td>Han Chinese, Thai</td>
<td>[17,31,32]</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>A<em>29, B</em>12, DR7</td>
<td>European</td>
<td>[30]</td>
</tr>
</tbody>
</table>

HLA, human leukocyte antigen.
29 Aug 2013: Recommendations for HLA-B*1502 genotype testing prior to initiation of carbamazepine in new patients

The Ministry of Health (MOH) has announced that genotyping for the HLA-B*1502 allele prior to the initiation of carbamazepine (CBZ) therapy in new patients of Asian ancestry is now considered the standard of care. These new recommendations by MOH and HSA have been made in consultation with experts in various fields such as neurology, psychiatry and dermatology, following the review of findings from local and international studies.

CBZ has been registered in Singapore since 1988 and is currently available as Tegretol® (Novartis (Singapore) Pte Ltd) and six generic products. It is indicated for the treatment of epilepsy and other conditions such as diabetic neuropathy, trigeminal neuralgia and bipolar disorders. While CBZ is an effective drug and the drug of choice for several conditions, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which are associated with significant mortality and long-term morbidity, have been reported with its use. Between 2003 and 2012, HSA received 131 local serious reports of CBZ-induced SJS/TEN (average of 15 reports per year). Since the beginning of this year, HSA has received five reports of SJS/TEN associated with the use of CBZ. A one-time HLA-B*1502 genotyping test helps distinguish high-risk patients who should avoid CBZ from low-risk patients who are able to continue to use this low-cost yet effective medicine.

SJS and TEN often begin with flu-like symptoms (fever, sore throat and fatigue), followed by development of a red or purplish rash and painful ulcers of mucous membranes. The skin lesions then progress to epidermal necrosis and detachment. SJS is diagnosed when epidermal detachment involves <10% of the body surface area, TEN when >30% of the body surface epidermal detachment is involved and SJS/TEN when 10-30% of the body surface epidermal detachment is involved. These conditions require hospitalisation and can be life-threatening and even fatal.
CORTICOSTEROIDS!

Full Offering of Both Brand & Generics

IVIG

Ciclosporin Mylan 100 mg
Corticosteroids in Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis: Current Evidence and Implications for Future Research

Ernest H. Law, BSc (Pharm), ACPR, BCPS, PharmD¹, and May Leung, BSc (Pharm), PharmD, BCPS²

Abstract

Objective: To review the evidence for the use of steroids in adults presenting with Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), or overlap. Data Sources: EMBASE (1974 to April 2014), MEDLINE (1946 to April 2014), Cochrane Database of Systematic Reviews, and International Pharmaceutical Abstracts (1970 to January 2014) were searched using the terms: prednisone, methylprednisolone, dexamethasone, prednisolone, steroids, glucocorticoids, corticosteroids, Stevens-Johnson Syndrome, toxic epidermal necrolysis, and SJS/TEN overlap. Study Selection and Data Extraction: English-language, full reports of experimental and observational studies were included. Bibliographies from pertinent publications were reviewed for additional references. Prespecified outcomes included survival, survival to discharge, hospitalization without intensive care, length of intensive care stay, duration of hospitalization, ophthalmological complications, infection rates, and adverse events. Data Synthesis: Six studies that used steroids for SJS, TEN, and/or overlap were included. All studies were retrospective cohort studies with no case-control or cross-sectional studies; 5 studies reported on steroid doses, and 2 studies reported time from disease onset to steroid use (2-4 days). Only 1 of 6 studies reported a statistically significant impact on mortality with steroids use (odds ratio = 0.4; 95% CI = 0.2-0.9). Adverse event rates were not reported in any of the studies. Conclusions: A review of the current evidence reveals a need for prospective, randomized controlled studies to provide more definitive conclusions on steroid use in patients with SJS, TEN, and/or overlap.
### Table 3. Systemic steroids for SJS/TEN (case series with ≥10 patients since 1994)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Number of patients</th>
<th>Disease</th>
<th>Treatment and dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criton (17)</td>
<td>1997</td>
<td>15</td>
<td>TEN average BSA 85%</td>
<td>High-dose steroids</td>
<td>0% mortality</td>
</tr>
<tr>
<td>Cheriyan (72)</td>
<td>1995</td>
<td>13</td>
<td>TEN 8 pts BSA &gt;80%</td>
<td>Methylprednisolone &gt;159 mg/day</td>
<td>0% mortality</td>
</tr>
<tr>
<td>Engelhardt (19)</td>
<td>1997</td>
<td>7</td>
<td>TEN</td>
<td>Burn center care</td>
<td>28% mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Steroids (dose unknown) + burn center</td>
<td>14% mortality</td>
</tr>
<tr>
<td>Kardaun (18)</td>
<td>2007</td>
<td>8</td>
<td>SJS (1) TEN (7)</td>
<td>Dexamethasone 1.5 mg/kg for 3 days</td>
<td>13% mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dexamethasone 100 mg/day + cyclophosphamide 500 mg × 1 day</td>
<td>0% mortality</td>
</tr>
<tr>
<td>Yamane (16)</td>
<td>2009</td>
<td>8</td>
<td>SJS (1) TEN (3)</td>
<td>Methylprednisolone (600–1000 mg/day)</td>
<td>13% mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Methylprednisolone (600–1000 mg/day)</td>
<td>22% mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Methylprednisolone +/- IVIG or plasmapheresis</td>
<td>0% mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Methylprednisolone +/- IVIG or plasmapheresis</td>
<td>25% mortality</td>
</tr>
</tbody>
</table>

BSA, body surface area; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.
The efficacy of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis: a systematic review and meta-analysis

Y.-C. Huang, Y.-C. Li and T.-J. Chen

1Department of Dermatology, Wu Feng Hospital, Taichung Medical University, 111 Xialing Road Section 3, Wenshan District, Taipei City 116, Taiwan
2Institute of Pharmacology, National Yang-Ming University, Taipei, Taiwan

Summary

Background Quantitative analysis of intravenous immunoglobulin (IVig) treatment against toxic epidermal necrolysis (TEN) is lacking.

Objectives To provide a meta-analysis evidence-based examination of IVig efficacy against TEN.

Methods A systematic review and meta-analysis of literature published before 31 July 2011 was conducted. In observational controlled studies with at least eight patients with TEN receiving IVig treatment, a pooled estimate of mortality risk was determined, comparing IVig and supportive care. Statistical analyses were performed on raw data to compare the clinical differences between (i) high-dose and low-dose IVig treatment in adult patients and (ii) paediatric and adult patients treated with IVig.

Results Seventeen studies met inclusion criteria. Overall mortality rate of patients with TEN treated with IVig was 19.9%. The pooled odds ratio (OR) for mortality from six observational controlled studies comparing IVig and supportive care was 1:00 [95% confidence interval (CI): 0.58–1:75; P = 0.99]. The pooled OR for mortality in patients treated with high-dose IVig vs. supportive care was 0.63 (95% CI 0.27–1.44; P = 0.27). Adults treated with high-dose IVig exhibited significantly lower mortality than those treated with low-dose IVig (18.9% vs. 50%, respectively; P = 0.022); however, multivariate logistic regression model adjustment indicated that IVig dose does not correlate with mortality (high vs. low dose: OR 0.894; 95% CI 0.106–2.000; P = 0.369). Paediatric patients treated with IVig had significantly lower mortality than adults (0% vs. 21.6%; P = 0.001).

Conclusions Although high-dose IVig exhibited a trend towards improved mortality and children treated with IVig had a good prognosis, the evidence does not support a clinical benefit of IVig. Randomized controlled trials are necessary.
Fig 2. Odds ratio (OR) of mortality associated with intravenous immunoglobulin treatment vs. supportive treatment. CI, confidence interval; M-H, Mantel–Haenszel methods. Experimental means intravenous immunoglobulin treatment and control means supportive treatment. For each study, central square indicates mean effect and line represents 95% CI. Large diamond represents combined ORs and 95% CIs of studies overall.
The role of intravenous immunoglobulin in toxic epidermal necrolysis: a retrospective analysis of 64 patients managed in a specialized centre

H.Y. Lee, Y.L. Lim, T. Thirumoothy and S.M. Pang

1Department of Dermatology, Singapore General Hospital, Outram Road, Singapore 169608
2National Skin Centre, Department of Dermatology, Singapore

Summary

Background. Toxic epidermal necrolysis (TEN) is a severe cutaneous adverse drug reaction with a mortality of 40%. Intravenous immunoglobulin (IVig) is widely used as a specific treatment for this reaction, although evidence of its benefit is conflicting.

Objectives. We sought to evaluate whether the use of IVig improved mortality in patients with Stevens–Johnson syndrome (SJS)/TEN overlap and TEN.

Methods. We retrospectively analysed data for 64 patients with SJS/TEN overlap and TEN who were treated with IVig at a single referral centre. The primary outcome analysed was in-hospital mortality. Predicted mortality was calculated based on severity-of-illness score for TEN (SCORTEN) values. Secondary analyses of survival based on IVig dosages and prior corticosteroid exposure were also performed.

Results. There were 28 cases of SJS/TEN overlap and 36 cases of TEN, with a mean SCORTEN value of 2.6. The mean dose of IVig given was 2.4 g kg\(^{-1}\) and the mean delay from the onset of epidermal detachment to administration of IVig was 3.2 days. There were 20 deaths (31%) in our cohort. The standardized mortality rate was 1.10 (95% confidence interval 0.62–1.58). Subgroup analysis comparing survivors and nonsurvivors showed a higher SCORTEN in nonsurvivors (3.4 vs. 2.2). There were no differences with regard to the dosage, delay and duration of IVig administration. When stratified according to dosage, there was no mortality difference between patients who receive high-dose (≥ 3 g kg\(^{-1}\)) vs. low-dose (< 3 g kg\(^{-1}\)) IVig.

Conclusions. This study shows that the use of IVig does not yield survival benefits in SJS/TEN overlap and TEN, even when corrected for IVig dosages.

What's already known about this topic?

- The use of intravenous immunoglobulin (IVig) in the treatment of toxic epidermal necrolysis (TEN) is controversial.

What does this study add?

- This study shows that the use of IVig in the treatment of Stevens–Johnson syndrome/TEN overlap and TEN does not yield survival benefits, even when corrected for IVig dosages and prior exposure to corticosteroids.
Open trial of ciclosporin treatment for Stevens–Johnson syndrome and toxic epidermal necrolysis

L. Valerye-Allanore, P. Wolkenstein, L. Brochard,* N. Ortonne,† B. Maître,‡ J. Revuz, M. Bagot and J.C. Roujeau

Department of Dermatology, Reference Centre for Toxic and Allergic Blistering Diseases, *Department of Medical Intensive Care Unit, †Department of Pathology and ‡Department of Pneumology, Hôpital Henri Mondor, Université Paris XII, F-94010 Créteil, France

Summary

Background Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute mucocutaneous reactions associated with poor prognosis. The treatment is mainly symptomatic, based on supportive care. Until now, several curative treatments have been proposed without evidence of effectiveness.

Objectives To evaluate the effect of ciclosporin on SJS and TEN after a short series had suggested a benefit.

Methods We conducted an open, phase II trial to determine the safety and possible benefit of ciclosporin. Among the 45 consecutive patients admitted for SJS/TEN from March 2005 to September 2007, 29 fulfilled inclusion criteria. Ciclosporin was administered orally (3 mg kg⁻¹ daily for 10 days) and tapered over a month. Clinical and biological evaluations were performed sequentially. Predicted death rate was estimated with a validated prognostic score (SCORTEN).

Results Twenty-nine patients were included at a mean ± SD of 2.8 ± 1.8 days after onset. The final diagnosis was SJS (n = 10), SJS/TEN overlap (n = 12) and TEN (n = 7). One month of treatment was completed in 26. Ciclosporin was stopped after more than 10 days in three cases for side-effects including posterior leukoencephalopathy (n = 1), neutropenia (n = 1) and nosocomial pneumonia (n = 1). Ciclosporin dosage was tapered earlier than scheduled in two cases for alteration in renal function. The prognostic score predicted 275 deaths; none occurred (P = 0.1). Mean epidermal detachment remained stable in 18 of 29 cases (62%). The mean ± SD hospital stay was 16.2 ± 9.1 days.

Conclusions Both the death rate and the progression of detachment seemed lower than expected, suggesting a possible usefulness of ciclosporin in SJS and TEN that needs to be confirmed.
Retrospective review of Stevens-Johnson syndrome/toxic epidermal necrolysis treatment comparing intravenous immunoglobulin with cyclosporine

Mark G. Kirchhof, MD, PhD, Monica A. Miliszewski, MD, Sheena Sikora, MD, Anthony Papp, MD, PhD, and Jan P. Dutz, MD

Vancouver, British Columbia, Canada

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are mucocutaneous reactions, typically to medications, that are associated with a high patient mortality. Controversy exists over which systemic treatments decrease mortality associated with SJS/TEN.

Objective: In this study we sought to determine whether intravenous immunoglobulin (IVIg) or cyclosporine use for SJS/TEN results in better patient outcomes.

Methods: We undertook a retrospective chart review of 71 patients admitted between 2001 and 2011 for SJS/TEN at a tertiary care center of which 64 cases were included in the data analysis. Predicted severity-of-illness score for TEN mortality was compared with actual mortality for patients treated with either cyclosporine or IVIg.

Results: Our cohort demonstrated a relative mortality benefit to the use of cyclosporine in the treatment of SJS/TEN with a standardized mortality ratio of 0.43, over the use of IVIg with a standardized mortality ratio of 1.43.

Limitations: This is single-center retrospective study.

Conclusions: The use of cyclosporine over IVIg may offer a greater mortality benefit in the treatment of SJS/TEN. (J Am Acad Dermatol 2014;71:941-7.)

Key words: cyclosporine; intravenous immunoglobulin; Stevens-Johnson syndrome; toxic epidermal necrolysis.
Table II. Predicted mortality of patients with Stevens-Johnson syndrome/toxic epidermal necrolysis using severity-of-illness score for toxic epidermal necrolysis versus observed mortality for patients treated with intravenous immunoglobulin or cyclosporine

<table>
<thead>
<tr>
<th>SCORTEN</th>
<th>IVIg</th>
<th>Cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Predicted mortality: 7.7 for IVIg, 2.4 for Cyclosporine

Observed mortality: 11 for IVIg, 1 for Cyclosporine

Standardized mortality ratio: 1.43 (95% CI 0.71-2.56) for IVIg, 0.42 (95% CI 0.11-2.32) for Cyclosporine

CI, Confidence interval; IVIg, intravenous immunoglobulin; SCORTEN, severity-of-illness score for toxic epidermal necrolysis.
<table>
<thead>
<tr>
<th>Initial assessment on presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Take a detailed history from the patient and/or relatives</td>
</tr>
<tr>
<td>• Perform a full physical examination, including baseline body weight and record the vital signs,</td>
</tr>
<tr>
<td>including oxygen saturation</td>
</tr>
<tr>
<td>• Order a set of investigations: FBC, U&amp;E, LFT, glucose, magnesium, phosphate, bicarbonate,</td>
</tr>
<tr>
<td>mycoplasma serology, CXR, skin biopsy and baseline body weight</td>
</tr>
<tr>
<td>• Initiate a primary management plan:</td>
</tr>
<tr>
<td>1. establish peripheral venous access</td>
</tr>
<tr>
<td>2. if patient cannot maintain adequate nutrition orally, insert a nasogastric tube and institute</td>
</tr>
<tr>
<td>nasogastric feeding</td>
</tr>
<tr>
<td>3. insert a urinary catheter if urogenital involvement is causing significant dysuria/retention</td>
</tr>
</tbody>
</table>

**(Strength of recommendation D (GPP))**

<table>
<thead>
<tr>
<th>Determination of drug causality</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Identify causative agent and withdraw immediately</td>
</tr>
</tbody>
</table>

**(Strength of recommendation D)**

<table>
<thead>
<tr>
<th>Prognostic scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Calculate SCORTEN within the first 24 h</td>
</tr>
</tbody>
</table>

**(Strength of recommendation C)**

---

Skin management regimen 1

Applicable to all patients in all settings

- Employ strict barrier nursing to reduce nosocomial infections
- Take swabs for bacterial and candidal culture from three areas of lesional skin, particularly sloughy or crusted areas, on alternate days throughout the acute phase
- Administer systemic antibiotics only if there are clinical signs of infection

(Significance of recommendation D (GPP))

Institute a conservative approach in all patients as follows:

- Regularly cleanse wounds and intact skin by irrigating gently using warmed sterile water, saline or an antimicrobial such as chlorhexidine (1/5000)
- Apply a greasy emollient, such as 50% white soft paraffin with 50% liquid paraffin (50/50 WSP/LP), over the whole epidermis, including denuded areas
- Apply a topical antimicrobial agent to sloughy areas only (choice should be guided by local microbiological advice). Consider Ag-containing products/dressings.
- The detached, lesional epidermis may be left in situ to act as a biological dressing. Blisters should be decompressed by piercing and expression or aspiration of tissue fluid.
- Apply non-adherent dressings to denuded dermis (suitable dressings include Mepitel™ or Telfa™).
- A secondary foam or burn dressing should be used to collect exudate (suitable dressings include Exu-Dry™).

Consider transfer to a Burn Centre in patients with TEN (> 30% BSA epidermal loss) and evidence of the following: clinical deterioration, extension of epidermal detachment, sub-epidermal pus, local sepsis, wound conversion and/or delayed healing. In a Burn Centre conservative measures may be supplemented with a surgical approach.

- Remove necrotic/loose infected epidermis and clean wounds using a topical antimicrobial agent (e.g. betadine or chlorhexidine) under general anaesthetic
- Consider debridement with Versajet™
- Physiological closure with Biobrane/allograft/xenograft skin in patients with early presentation involving non infected and large confluent areas

(Significance of recommendation D (GPP))

Skin management regimen 2

This may involve a conservative and/or surgical approach based on the specialist multi-disciplinary team’s daily review of the individual needs of the patient
Summary

• A detailed medication history is essential in suspected drug reactions

• Document the drug reaction in the patient’s chart with the medication and description of the reaction

• Exanthematous eruptions are the most common of all cutaneous drug eruptions and tend to resolve without sequelae

• Fixed drug eruptions will recur at the same with re-exposure to the drug
Summary

• SJS and TEN are acute life-threatening mucocutaneous reactions characterized by extensive necrosis and detachment of the epidermis and mucosal surfaces

• Consult dermatology at the earliest moment of concern for SJS/TEN

• Cessation of culprit drug/ supportive care of skin and affected organs/ IVIG vs Ciclosporin
Fighting for 66 Days
Aug 17, 2015 | Care integration

Jocelyn Suarez

My recent brush with death put me on the other side of the bed. I went from fit young nurse tending to patients to one lying helpless in bed, being tended - Jocelyn Suarez, Singapore Health Inspirational Patient Award 2015
In November 2013, my eyes swelled and I developed fever and rashes after taking a common painkiller-antibiotic. I consulted the doctor with what I thought was a simple allergic reaction or virus infection.

However, I was warded as the symptoms grew worse. I had swollen lips and was itching badly everywhere. The next thing I knew, I was waking up in the Intensive Care Unit three weeks later! I had contracted a rare and life-threatening skin condition which also affects the mucous membrane - Toxic Epidermal Necrolysis.

It was a rude shock to be so ill. After all, I was a nurse, young and invincible.

The illness affected almost every part of my body. I swelled to twice my usual size and had to undergo dialysis. My eyes were blurry; I couldn’t breathe easily, couldn’t speak or eat and could barely move. It hurt everywhere.

My road to recovery was rough. There were complications which put me back in the hospital a day after my discharge. In total, I spent 66 days in the hospital fighting for my life.

During the drug-induced days when I was hardly conscious, I remember being pulled out of a dream by gentle hands.
As I slowly regained my strength, I really appreciated the doctors and nurses who cared for me. I was more than just a case or illness to them – they treated me with love, kindness and respect and I will forever be thankful for that.

My family and friends were a huge pillar of support. Seeing their faces every morning gave me hope. I heard they even arranged a fund-raiser event to help with my huge medical expenses. It astounded me that there were people who cared enough to help me. It’s the kind of the thing that restores one’s faith in humanity.

Today, Jocelyn has gone back to work as a nurse and has even been actively participating in marathons.
Treatment Areas

- WRI > Wrinkle Relaxing Injections – DF > Dermal Fillers
  - Forehead, Worry Lines, Crease (WRI & DF)
  - Glabellar Frown Lines (WRI)
  - Eyebrows - Lift (WRI)
  - Crow’s Feet (WRI & DF)
  - Undereyes – Fill (DF)
  - Bunny Lines – Soften (WRI)
  - Cheeks – Lift/Contour (DF)
  - Nasolabial Folds (DF)
  - Vertical Lip Lines (WRI & DF)
  - Lips – Enhance/Define (DF)
  - Corners of Mouth – Lift/Upturn (WRI & DF)
  - Marionette Lines – Mouth/Chin (DF)
  - Jawline – Define (DF)
  - Neck Bands/Creases – Smooth (WRI)
  - Chin Creases – Smooth (WRI)