STUDY

Analysis of Intravenous Immunoglobulin for the Treatment of Toxic Epidermal Necrolysis Using SCORTEN

The University of Miami Experience

Jennifer T. Trent, MD; Robert S. Kirsner, MD; Paolo Romanelli, MD; Francisco A. Kerdel, BSc, MBBS

Background: Toxic epidermal necrolysis (TEN) is a rare, life-threatening condition caused by certain medications. Keratinocytes affected by TEN have been found to undergo apoptosis mediated by Fas-FasL interactions. Treatment with intravenous immunoglobulin (IVIG) has been proposed to inhibit this interaction.

Objective: To demonstrate the effectiveness of IVIG therapy in reducing mortality in patients with TEN.

Design: A retrospective analysis of 16 consecutive patients with TEN who were treated with IVIG. The SCORTEN system, a validated predictor of TEN mortality, was used to analyze the data of these patients. Using SCORTEN, we compared the predicted mortality of our patient population with observed mortality.

Setting: Dermatology inpatient unit at a university-affiliated hospital.

Intervention: All 16 patients received IVIG treatment daily for 4 days. Fifteen patients received 1 g/kg per day and 1 patient received 0.4 g/kg per day.

Main Outcome Measures: For each patient, causes of TEN and other medical problems were documented prior to IVIG therapy, as were the 7 independent SCORTEN risk factors.

Results: One patient died. Based on the SCORTEN system, 5.81 patients were expected to die. These mortality rates were compared using the standardized mortality ratio (SMR) analysis ([Σ observed deaths/Σ expected deaths] × 100) to determine the efficacy of this treatment, which showed that patients with TEN treated with IVIG were 83% less likely to die than those not treated with IVIG (SMR=0.17; 95% confidence interval, 0.0-0.96).

Conclusion: Based on comparison of our observed mortality rate with the SCORTEN-predicted mortality rate, treatment with IVIG significantly decreased mortality in patients with TEN.

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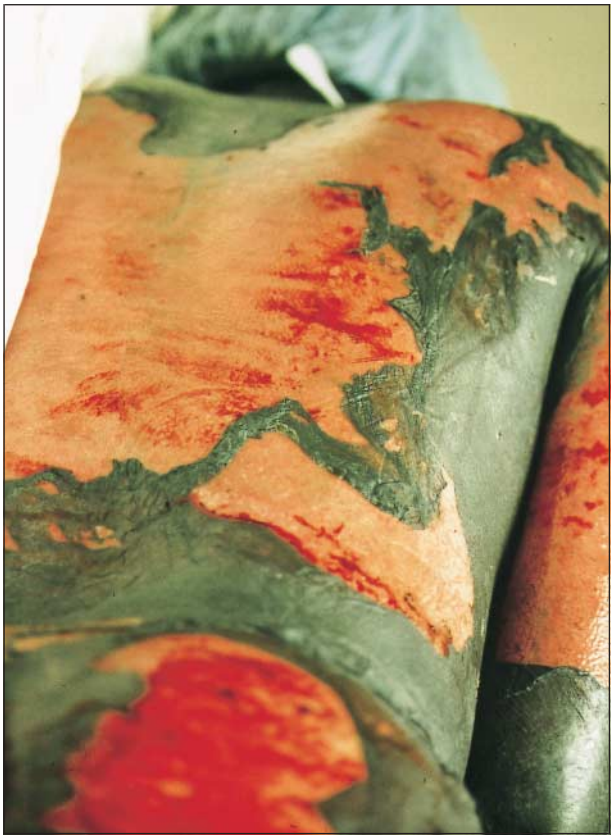
From the Departments of Dermatology and Cutaneous Surgery (Drs Trent, Kirsner, Romanelli, and Kerdel) and Epidemiology and Public Health (Dr Kirsner) and the Veterans Administration Medical Center (Dr Kirsner), University of Miami School of Medicine, Miami, Fla.

TOXIC EPIDERMAL necrolysis (TEN) is a rare, life-threatening condition, the result of a hypersensitivity reaction to various drugs.[1-3] The incidence of TEN varies between 0.4 and 1.2 cases per million per year, and more than 100 different drugs have been associated with TEN.[1] The mortality rate associated with TEN varies from 15% to 40%, with a large portion of patients dying from infections or multiorgan failure.[2-4]

Toxic epidermal necrolysis often begins with symptoms of fever, sore throat, and burning eyes, usually 1 to 3 days prior to any cutaneous lesions.[4] The cutaneous signs emerge as poorly defined erythematous macules with darker purpuric centers that tend to merge and cause extensive epidermal necrosis and detachment (**Figure**). Mucosal lesions are invariably present and usually involve the conjunctiva, mouth, trachea, bronchi, genitourinary tract, and parts of the gastrointestinal tract. Histologic examination shows necrotic keratinocytes and confluent epidermal necrosis with vacuolar alteration of the dermoepidermal junction and subepidermal blisters.[5]

See also pages 26, 33, and 85

Recent discoveries have shown that keratinocytes in TEN undergo apoptosis, not simply necrosis.[6,7] Further research has elucidated that this apoptosis can be induced by interactions between cell-surface death receptor Fas and its ligand, FasL or CD95L.[7] Keratinocytes express little FasL under normal conditions; however, in TEN there is a 3- to 4-fold upregulation of the FasL. Keratinocytes usu-



Extensive cutaneous involvement of toxic epidermal necrolysis in patient 7 prior to beginning intravenous immunoglobulin treatment.

ally express Fas, and their numbers remain unchanged during TEN.

It is known that intravenous immunoglobulin (IVIG) treatment, among other things, inhibits Fas-mediated keratinocyte apoptosis by blocking the Fas receptor. In a recent study by Viard et al,[7] 10 patients with TEN were treated with IVIG. The authors suggest that IVIG may abrogate the process of epidermal necrolysis and decrease mortality. We report the prospective use of IVIG in 16 patients with TEN at a single institution. Eight patients (patients 1-5, 8, 10, and 11) were also included in a previous multicenter retrospective study.[8]

SCORTEN, a TEN-specific severity of illness scale, has been proven to be an accurate predictor of mortality in patients with TEN[9] by evaluating 7 independent risk factors (age >40 years; presence of malignancy; body surface area involved >10%; serum urea nitrogen level >28 mg/dL [>10 mmol/L]; glucose level >252 mg/dL [>14 mmol/L]; bicarbonate [HCO_3] level <20 mEq/L [<20 mmol/L]; and heart rate >120 beats per minute within the first 24 hours of admission). To evaluate the efficacy of IVIG treatment for our patients with TEN, we used the SCORTEN scale.

METHODS

Sixteen patients with TEN were included in this study. Patients with Stevens-Johnson syndrome were excluded because they usually have good outcomes (<2% mortality). All patients were admitted to the dermatology unit at the University of Miami Department of Dermatology/Cedars Medical Center. Diagnosis was based on clinical findings and confirmed with findings of skin biopsy analysis. The drug responsible for the condition was determined historically according to the timing of the drug reaction.

The patients were managed with our standard TEN protocol, which included nonstick dressings impregnated with isotonic sodium chloride solution (normal saline) or silver nitrate every 3 to 8 hours and changed every 3 days.[10] Hematologic, electrolyte, and blood chemistry values was closely monitored. Biopsies and wound cultures were performed on admission. Pain control, antacids, oral hygiene, anticoagulants, and systemic and ophthalmic antibiotics were administered as needed by the patient. In some cases, ventilatory support (including endotracheal intubation and/or tracheostomy), dialysis, blood transfusions, and/or filgrastim treatments were necessary. Aggressive pulmonary toilet was undertaken on all patients. Adequate nutrition for the hypermetabolic state was achieved via a nasogastric tube in most patients, but some patients required total parenteral nutrition. A dose of 1 g/kg of IVIG was administered in all cases (except for patient 8, who received 0.4 g/kg) every day for 4 days. All but 2 patients (patients 8 and 9) received IVIG without sucrose, which is nephrotoxic. Patient 8 had end-stage renal disease prior to receiving the IVIG and was undergoing hemodialysis. Patient 9 had normal renal function prior to receiving IVIG and did not develop any renal insufficiency. Clinical data for the 16 patients are reported in **Table 1** and **Table 2**.

Each of the SCORTEN risk factors was recorded for each of the 16 patients treated with IVIG (**Table 3** and **Table 4**). The predicted mortality percentage was based on the number of risk factors each patient possessed. Patients with 0 to 1 risk factors had an expected mortality rate of 3.2%; 2 risk factors, 12.2%; 3 risk factors, 35.3%; 4 risk factors, 58.3%; and 5 or more risk factors, 90%. The expected number of deaths was calculated for each subgroup. The standardized mortality ratio analysis (SMR) ($[\Sigma \text{ observed deaths}/\Sigma \text{ expected deaths}] \times 100$) was used to determine whether IVIG treatment could significantly reduce mortality for patients with TEN.[11]

RESULTS

The average age of the patients was 42.81 years (range, 19-62 years). There were 8 men and 8 women. Six patients were Hispanic, 4 were white, 5 were black, and 1 patient was Indian. In regard to medical history, 4 of the patients had metastatic disease and/or tumor, and 5 patients had human immunodeficiency virus (HIV). One patient was pregnant and gave birth, without complications, to a healthy baby through normal spontaneous vaginal delivery.[12] Cases were classified according to a recently published classification system into Stevens-Johnson syndrome/TEN overlap, TEN with spots, and TEN without spots, depending on the percentage of body surface area involvement and characteristic cutaneous findings.[13] Phenytoin was the causal agent in 6 of the cases. Also, HIV drugs were the causal agent in 5 of the cases. The average length of stay in the hospital was 20.31 days. No further lesions developed subsequent to IVIG treatment after an average of 3.75 days, with total reepithelialization occurring in an average of 8.50 days. The average time between the first cutaneous lesion and the start of IVIG treatment was 3.50 days.

Findings of hematologic analysis showed large variation among patients. White blood cell counts ranged from 1.7 to $32.6 \times 10^3/\mu L$, hemoglobin from 7.3 to 15.9 g/dL,

Table 1. Patient Data

Patient No./ Sex/Age, y	Race	Medical History	Category of TEN	Offending Drug	% BSA
1/M/43	Black	HIV, CVA	SJS/TEN overlap	Trimethoprim-sulfamethoxazole	30
2/M/62	White Latin	Glioblastoma multiforme, HTN, DM	TEN with spots	Phenytoin	40
3/M/34	Black	HIV, DM	TEN with spots	Nevirapine	30
4/M/38	White	Mets colon cancer	TEN	Vancomycin	>90
5/M/45	White Latin	HTN, DM, CHF, CAD	TEN	Allopurinol	70-90
6/M/47	White	Mets melanoma	TEN	Phenytoin/lamivudine (15.0 mg)-zidovudine (300 mg)	70
7/F/26	Black	HIV, pregnant 30 wk	TEN with spots	Nelfinavir	60
8/F/48	Indian	DM, ESRD	TEN with spots	Furosemide	30
9/F/47	White Latin	Elevated uric acid	SJS/TEN overlap	Allopurinol	27
10/M/60	White	Mets lung cancer	SJS/TEN overlap	Phenytoin	25
11/F/54	White	CVA, HTN, seizures	TEN	Phenytoin	60
12/F/38	Black	HIV, Bell palsy	SJS/TEN overlap	Sulfadiazine	12
13/F/33	White Latin	Cerebral aneurysm with clip, SAH	SJS/TEN overlap	Phenytoin	40
14/F/46	White Latin	Chronic meningitis, Graves disease	TEN	Butalbital-acetominophen-caffeine	30
15/F/19	White Latin	Seizures	TEN with spots	Phenytoin	30
16/M/45	Black	HIV, PCP, pancreatitis	SJS/TEN overlap	Trimethoprim-sulfamethoxazole	28

Abbreviations: BSA, body surface area; CAD, coronary heart disease; CHF, congestive heart failure; CVA, cerebrovascular accident; DM, diabetes mellitus; ESRD, end-stage renal disease; HIV, human immunodeficiency virus; HTN, hypertension; Mets, metastasis; PCP, *Pneumocystis carinii* pneumonia; SAH, subarachnoid hemorrhage; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

hematocrit from 21.0% to 45.5%, and platelet counts from 55 to 593 × 10^3/μL. Serum chemical analyses showed variable results as well, with serum urea nitrogen ranging from 4 to 137 mg/dL (1.4-48.9 mmol/L) and creatinine from 0.5 to 8.2 mg/dL (44.2-724.9 mmol/L). Serum phosphorus values ranged from 1.2 to 7.9 mg/dL (0.39-2.55 mmol/L) and albumin from 1.0 to 4.8 g/dL.

Of the 16 patients in this study, all showed clinical improvement and disease resolution. However, there was 1 death due to preexisting medical conditions. The patient (patient 8) had been undergoing dialysis prior to contracting TEN and received a lower dose of IVIG (0.4 mg/kg per day for 4 days) than the other patients received. Despite this lower dose, the patient's lesions resolved, but she experienced a fatal episode of asystole. None of the other patients developed complications, and IVIG therapy was well tolerated. Abnormalities in laboratory values normalized after resolution of TEN in all patients. One patient required a tracheostomy to treat respiratory failure secondary to adult respiratory distress syndrome.

Based on SCORTEN, the expected mortality was 5.81 patients or 36.3%. However, the actual mortality was 1 patient or 6.25%. The SMR analysis indicated an 83% reduction in mortality for patients treated with IVIG (SMR=0.17; 95% confidence interval, 0.0-0.96).

Table 2. Patient Outcome Data

Patient No.	Cessation of Lesions After Starting IVIG, d	Time to Total Reepithialization, d	Outcome	Days in Hospital
1	2	4	Alive	56
2	5	12	Alive	29
3	17	23	Alive	26
4	2	5	Alive	14
5	6	18	Alive	40
6	2	10	Alive	37
7	2	7	Alive	13
8	4	11	Dead	16
9	3	8	Alive	12
10	1	4	Alive	7
11	5	5	Alive	11
12	2	5	Alive	9
13	2	5	Alive	11
14	2	7	Alive	16
15	4	7	Alive	14
16	1	5	Alive	14

Abbreviation: IVIG, intravenous immunoglobulin.

COMMENT

Toxic epidermal necrolysis is a life-threatening exfoliative condition, usually the result of a severe drug reaction involving the apoptotic loss of the epidermis.[6] Many drugs have been implicated in the pathogenesis of TEN.[1] In a large case-controlled study, the drugs most commonly associated with TEN were found to be sulfonamides, anticonvulsant agents, allopurinol, and oxicam nonsteroidal anti-inflammatory drugs.[1,3] There is also substantial association with antibiotics such as cephalosporins, quinolones, aminopenicillins, tetracyclines, and imidazole antifungal agents. Recently, a study suggested that the sooner the drug treatment was halted, the fewer skin lesions would occur, and consequently the lower the mortality rate would be.[4] It was demonstrated that the early cessation of treatment with the causative drug would decrease mortality from 27% to 11%. However, this only held true for drugs with short half-lives. Those with longer half-lives are associated with the same mortality regardless of how soon the treatment is discontinued.

The diagnosis of TEN is based on clinical appearance and histopathologic evaluation. Standard management in our service includes discontinuation of treatment with the suspected drug, fluid replacement including colloids, strict intake and output, use of nonstick dress-

Table 3. SCORTEN Data*

Patient No.	Age, y (>40 y)	Malignancy	BSA, % (>10%)	Bicarbonate, mEq/L (<20 mEq/L)	Glucose, mg/dL (>252 mg/dL)	Serum Urea Nitrogen, mg/dL (>28 mg/dL)	Pulse Rate (>120/min)	Score
1	43		30	26	181	94	125	4
2	62	Glioblastoma	40	23	158	19	134	4
3	34		30	26.2	107	20	133	2
4	38	Mets colon cancer	>90	25.9	111	24	121	3
5	45		70-90	17	745	98	127	6
6	47	Mets melanoma	70	26.3	211	22	134	4
7	26		60	22.2	77	5	122	2
8	48		30	19.7	264	38	123	6
9	47		27	27	116	15	88	2
10	60	Mets lung cancer	25	26.1	99	13	86	3
11	54		60	23.9	111	9	121	3
12	38		12	25	89	20	121	2
13	33		40	22	164	10	128	2
14	46		30	24	109	13	92	2
15	19		30	25	97	9	124	2
16	45		28	20	127	10	122	3

Abbreviations: BSA, body surface area; Mets, metastasis; SCORTEN, a severity-of-illness score for toxic epidermal necrolysis.
SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.5551; serum urea nitrogen to millimoles per liter, multiply by 0.357.
*Values in parentheses represent risk for death.

Table 4. Mortality Data

SCORTEN	No. of Patients	Expected Mortality		Observed Mortality	
		%	Rate	%	Rate
0-1	0	3.2	0	0	0
2	7	12.1	0.847	0	0
3	3	35.3	1.412	0	0
4	3	58.3	1.749	0	0
≥5	2	90.0	1.800	50	1
Total	**16**	. . .	**5.808**	. . .	**1**

Abbreviation: SCORTEN, a severity-of-illness score for toxic epidermal necrolysis.

ings soaked with normal saline or 0.5% silver nitrate, systemic administration of antibiotics as per wound cultures, nutritional support, pulmonary and eye care, analgesics, anticoagulation, antacids, and/or (recently) IVIG.[9] Depending on the complications due to TEN, it is often necessary to provide ventilatory support, dialysis, transfusions, and/or filgrastim treatment. Some patients require transfer to the intensive care unit.

In the past, IVIG has been used to treat a number of autoimmune disorders, including dermatologic diseases such as dermatomyositis and pemphigus.[14] It is known that IVIG modulates cytokine release, induces blockade of receptors, and inhibits Fas-mediated keratinocyte apoptosis.[7] In 1998, Viard et al[7] suggested that IVIG could be used to treat TEN. It works by inhibiting keratinocyte apoptosis triggered by interaction with cell surface death receptor Fas with FasL. In the study by Viard et al,[7] patients with TEN were treated with 0.2 to 0.75 g/kg of IVIG every day for 4 days. This regimen was sufficient to cause resolution of TEN without any complications. Later, other case reports supported the use of IVIG to treat patients with TEN.[15-20] In these cases, there was rapid improvement, shorter hospital stays, and no mortalities. Intravenous immunoglobulin treatment provides a large colloidal source of protein with a longer half-life than albumin (17 days vs 6 hours), and we believe that colloidal intravenous support is very important in the early stages of TEN, thus IVIG may have additional benefit.

In contrast to our previous experience with TEN spanning over a decade, where our mortality rate was 29% prior to the use of IVIG, our recent experience with IVIG adds further support for its use in TEN (**Table 5**). In the present study, all 16 patients with TEN were successfully treated as shown by disease resolution and clinical improvement. One patient died, but this was the result of the patient's preexisting condition. Lower doses of IVIG (2 g/kg total) have been linked to increased risk of mortality.[8] Interestingly, 14 of our patients received a full dose of IVIG (4 g/kg total) and survived. In addition, IVIG was well tolerated in all patients.

SCORTEN, a TEN-specific illness severity score, was used to assess the value of IVIG for patients with TEN. SCORTEN has been shown to be effective in predicting mortality rates in patients with TEN based on 7 independent risk factors (age, >40 years; presence of malignancy; body surface area involved, >10%; serum urea nitrogen level, >28 mg/dL [>10 mmol/L]; glucose level,

Table 5. Mortality Prior to Institution of Intravenous Immunoglobulin Therapy*

Diagnosis	No. of Patients	No. (%) of Actual Deaths
SJS/TEN overlap	7	0
TEN with spots	13	3 (23)
TEN	8	5 (63)
Total	**28**	**8** (29)

Abbreviations: SCORTEN, severity-of-illness score for TEN; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
*SCORTEN predictions are not available for this subset.

>252 mg/dL [>14 mmol/L]; bicarbonate [HCO_3] level, <20 mEq/L [<20mmol/L]; and heart rate, >120 beats per minute within the first 24 hours of admission).[9] The mortality rate for patients is based on the number of risk factors each patient has. The SCORTEN system predicted 5.81 deaths, but there was only 1 death. The SMR analysis ([Σ observed deaths/Σ expected deaths] $\times$ 100) was used to compare the observed and expected mortality rates based on the SCORTEN system. The calculated SMR of 0.17 (95% confidence interval, 0.0-0.96) showed that patients treated with IVIG were 83% less likely to die, based on SCORTEN, than those patients who were not treated with IVIG ($P<.05$).

In conclusion, we add support to the use of IVIG in the treatment of patients with TEN. Using predicted mortality as determined by the SCORTEN system, IVIG treatment significantly decreased mortality and was well tolerated. Until a randomized placebo-controlled trial of IVIG for patients with TEN is performed, our data support the use of IVIG for patients with TEN.

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Corresponding author and reprints: Francisco A. Kerdel, BSc, MBBS, University of Miami Department of Dermatology, PO Box 016250, Miami, FL 33136 (e-mail: dermatology.department@hcahealthcare.com).

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News and Notes

The Photomedicine Society Meeting will be held March 20, 2003, in San Francisco, Calif. For more information, fax Susan Milberger at (214) 648-0280 or e-mail at susan.milberger@utsouthwestern.edu (Web site: www.photomedicine.org).