
CME review article

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Pathogenesis and recent therapeutic trends in Stevens-Johnson syndrome and toxic epidermal necrolysis

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Objective: To review the current pathophysiologic mechanisms and recent therapeutic trends in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Data Sources: A MEDLINE search for SJS and TEN in combination with Fas, Fas ligand (FasL), cytotoxic T cells, intravenous immunoglobulin, and cyclosporine for articles published in English during 1966 to 2006.

Study Selection: Information was derived from original research articles and reviews published in peer-reviewed journals.

Results: The hallmark of SJS and TEN is epidermal cell apoptosis, which may be mediated through keratinocyte Fas-FasL interaction or through cytotoxic T-cell release of perforin and granzyme B. Whereas systemic corticosteroid therapy showed contradictory results, intravenous immunoglobulin (IVIG) and cyclosporine have shown promising outcomes. IVIG contains anti-Fas antibodies that can abrogate apoptosis when preincubated with keratinocytes. Most studies on IVIG in SJS and TEN reported improvement in arresting disease progression and reduction in time to skin healing. Because of variations among studies, the findings cannot be optimally compared. In general, mortality varied from 0% to 12% in studies that supported the use of IVIG and 25% to 41.7% in those that did not demonstrate a beneficial effect. Cyclosporine inhibits CD8 activation and thus may reduce epidermal destruction. Relatively few case reports and 1 case series have been published regarding the use of cyclosporine in SJS and TEN. In general, cyclosporine was associated with a significant improvement in time to disease arrest and to complete reepithelization, with no reported fatalities.

Conclusions: Both IVIG and cyclosporine have been associated with enhanced healing and better survival through inhibition of apoptosis. Multicenter, randomized, placebo-controlled trials using a standardized design are needed to validate these findings.

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INTRODUCTION

Erythema multiforme, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), which were initially described as separate entities, are now considered a continuum of the bullous disease syndromes in which keratinocyte cell death results in subepidermal separation. The disease is usually caused by infections or medications, most commonly antibacterial sulfonamides, anticonvulsants, nonsteroidal an-

ti-inflammatory drugs, and allopurinol.¹ A prodrome of fever and malaise is usually followed by a vesiculobullous eruption, whereby stroking on the skin induces epidermal separation (Nikolsky sign). There is no universally accepted definition of the syndrome, but the presence of mucosal involvement and the percentage of body surface area (BSA) involved can help in classifying the clinical condition (Table 1).² Skin biopsy specimens from affected areas typically show epidermal necrosis (necrolysis) with a sparse dermal monocyte (predominantly T-cell) infiltrate.²

Despite a high prevalence of the causative factors, the current estimated annual incidence of SJS and TEN ranges from 0.4 to 7 per million population.³⁻⁶ Although generally

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Table 1. Clinical Classification of SJS and TEN*

Category	Skin lesion	Epidermal detachment, % of BSA
SJS	Widespread; macules with blisters or flat atypical targets; mucosal erosions	<10
SJS-TEN overlap	Widespread; macules with blisters or flat atypical targets; mucosal erosions	10–30
TEN	Widespread; macules with blisters or flat atypical targets; mucosal erosions	>30

Abbreviations: BSA, body surface area; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

* Modified from Paquet et al.²

rare, SJS and TEN are important because of their high morbidity and mortality, with the latter ranging from 1% to 5% in SJS^{7,8} and 25% to 35% in TEN.^{5,8,9} The standard of care has been immediate discontinuation of use of the offending drug and prompt initiation of aggressive, multidisciplinary supportive care. Systemic corticosteroid therapy is not in the domain of this review. Its use has been reported as useful by some^{10–12} and harmful by others^{13,14} and therefore remains controversial.

Specific effective treatments for SJS and TEN are lacking, in part because of our unclear understanding of the pathophysiology of these blistering skin diseases. Consequently, the mortality has not substantially improved. During the past 10 years, medical researchers have made significant progress in elucidating the mechanisms of this syndrome. The objective of this article is to review the current understanding of SJS and TEN pathophysiology and recent trends in therapy based on our improved knowledge of the possible mechanism of disease. We performed a MEDLINE search for SJS and TEN in combination with Fas, Fas ligand (FasL), cytotoxic T cells, intravenous immunoglobulin (IVIG), and cyclosporine for articles published in English during 1966 to 2006. Information was derived from original research articles and reviews published in peer-reviewed journals.

PATHOPHYSIOLOGY

Whereas cell death by necrosis is a disorganized, nonspecific process, apoptosis is a programmed cell death that results from one of many possible mechanisms. Ligation of various cell surface death receptors, including tumor necrosis factor (TNF), Fas, and TNF-related apoptosis-inducing ligand, can trigger activation of the caspase system, leading to DNA disassembly and cell death. Alternatively, there are death receptor-independent mechanisms. In particular, cytotoxic T cells can express and release perforin and granzyme B, which can cause apoptosis in either caspase-dependent or caspase-independent mechanisms. Epidermal cell death and sloughing seen in TEN have been shown to result from apoptosis.¹⁵ A few mechanisms have been proposed for epidermal cell apoptosis seen in SJS and TEN, including Fas-FasL interaction,^{16,17} cytotoxic T cells,^{18,19} TNF- α ,^{15,20} and nitric oxide synthase.²¹ The first 2 mechanisms are generally considered to be more likely and will be the focus in this review.

Fas-FasL Interaction

Virtually all cells, including epidermal cells (keratinocytes), express Fas on their cell surfaces; however, its ligand (FasL)

is mainly expressed on T cells and natural killer cells.²² For Fas-FasL interactions to play a role, lytically active FasL must be expressed at the site of epidermal cell death. To this end, Viard et al¹⁶ conducted a landmark study that popularized the Fas-FasL interaction as a significant pathophysiologic mechanism. The investigators screened serum samples from a group of patients with histologically proven TEN, drug-induced maculopapular rash, and healthy controls for soluble FasL (sFasL). They reported that sFasL elevation and FasL expression in skin biopsy specimens were present only in patients with TEN. They concluded that the sFasL detected in the sera resulted from cleavage of a membrane-bound FasL on the epidermal cells. Having established the physical presence of both Fas and FasL in the epidermis, the authors then studied the lytic capacity of keratinocytes in vitro by overlaying frozen skin sections from the 3 groups with Fas-sensitive Jurkat cells (a T-cell leukemia cell line). Measuring Jurkat cell apoptosis with a fluorescein assay, they found that TEN skin sections induced 3 to 4 times more Jurkat cell death. In addition, apoptosis was abrogated when TEN skin sections were preincubated with a FasL-blocking antibody. The authors concluded that TEN keratinocytes express lytically active FasL and that the ligation of keratinocyte-expressed Fas leads to apoptosis.

The 1988 study by Viard et al created significant interest in keratinocyte apoptosis mediated by Fas-FasL interaction. However, the authors did not directly prove that FasL-expressing keratinocytes could kill adjacent Fas-expressing keratinocytes. Rather, it was inferred based on the effect of Jurkat cells, which are known to overexpress Fas. Keratinocytes, however, have not been shown to overexpress Fas.^{23,24} In fact, keratinocytes are 10-fold less susceptible to sFasL-induced apoptosis than are Jurkat cells. This has led other researchers to suggest that keratinocyte FasL acts as a defense against lymphocytic attack rather than the mechanism of apoptosis.²⁵

The source of sFasL was called into question recently, because only 1 study¹⁶ had reported epidermal FasL expression in vivo. Abe et al²⁶ analyzed serum samples from patients with SJS, TEN, erythema multiforme type drug eruption, and healthy controls. They found significantly elevated sFasL concentrations only in SJS and TEN. Using monoclonal antibody (mAb) to FasL, they found no membrane-bound FasL expression on keratinocytes in TEN patients or in healthy controls. Furthermore, sFasL levels increased significantly when peripheral blood mononuclear cells (PBMCs)

from TEN patients were cultured with the offending drug. Coculture with anti-FasL mAb significantly reduced the number of apoptotic cells in a dose-dependent manner, suggesting a Fas-FasL mediated apoptosis. They concluded that sera from patients with SJS and TEN induce apoptosis mediated by PBMC-derived FasL. Unlike the report by Viard et al,¹⁶ Abe et al found no evidence to support lytically active FasL on keratinocytes.

A follow-up study by Viard-Leveugle et al¹⁷ shed some light on these contradictory findings. Using reverse-transcriptase polymerase chain reaction, the authors demonstrated that FasL was confined to the basal and suprabasal layers of normal human epidermis. Despite demonstrating both Fas and FasL coexpression in the lower dermis and Fas death-signaling functionality, keratinocyte FasL was incapable of causing apoptosis. Using in vitro and ex vivo assays, the authors were able to prove that keratinocyte FasL is predominantly cytoplasmic in vivo and is completely absent from the cell surface. This may explain the absence of spontaneous skin death despite colocalization of Fas and FasL in normal epidermis. However, it does not explain how FasL is involved in TEN. The authors postulated that FasL may be transported to the cell surface to effect apoptosis in TEN. Abe et al,²⁶ however, observed that TEN skin sections failed to express FasL. It is worth noting that their conclusion was based on skin specimens from only 3 TEN patients. It is also conceivable that FasL-expressing keratinocytes had already undergone apoptosis in the examined specimens. Alternatively, keratinocyte intracellular FasL may not be induced to extracellular expression and may not be involved in TEN as postulated by Viard-Leveugle et al.¹⁷

Nassif et al²⁴ have also contributed to our understanding of the role of Fas-FasL interaction. They found higher concentrations of interferon- γ (IFN- γ), TNF- α , and sFasL in blisters of TEN patients than in "control" blister fluid from burn patients. IFN- γ is known to increase TNF- α and sFasL levels and cause keratinocyte activation.²⁷ Interestingly, blister fluid lymphocytes did not express more sFasL than control lymphocytes. The authors inferred that sFasL originated from the keratinocyte; in fact, they subsequently demonstrated keratinocyte FasL overexpression in situ. In addition, blister fluid lymphocytes showed much stronger binding to granzyme B antibody than to FasL antibody (85% vs 3%). Keratinocytes incubated with cell-free supernatant of TEN blister fluid showed keratinocyte activation without apoptosis. This suggests the presence of sufficient IFN- γ to cause activation but insufficient sFasL to cause apoptosis. This should not be surprising since blister fluid sFasL concentration is generally on the order of 5 ng/mL, whereas the concentration of human recombinant sFasL (rhsFasL) necessary to cause keratinocyte apoptosis is much higher (inhibitory concentration that results in a 50% reduction in proliferation = 89 to 232 ng/mL).¹⁷

Unexpectedly, Fas expression was not present on all subcorneal layers but restricted to the epidermal basal keratinocytes. This has been reported by other researchers as well,

who concluded that it is difficult to attribute full-thickness epidermal destruction to Fas activation alone.²³

Although the proposed Fas-FasL mechanism has its appeal, several questions remain unanswered: (1) What is the source of sFasL? (2) Is the sFasL lytically active? (3) Are Fas and FasL coexpressed in the same areas of epidermis to facilitate full-thickness destruction? (4) Does FasL play a role in TEN apoptosis? Further studies are needed to clarify such issues.

Cytotoxic T Cells

Discovery of drug-specific T-cell clones from the skin cells of patients with drug eruptions has generated interest in drug-specific cytotoxicity by CD8 lymphocytes as an alternative mechanism for apoptosis in TEN.^{28,29} A prominent role of CD8 cells does not necessarily exclude Fas-FasL mediated apoptosis, because cytotoxicity is accomplished through 2 major pathways: granule-mediated exocytosis of perforin and granzyme B and Fas-FasL ligation.

Posades et al¹⁹ studied 15 patients with drug-induced, delayed rash to determine the degree of involvement of these 2 cytotoxic pathways. Using competitive reverse-transcriptase polymerase chain reaction, they quantitated the specific transcription of TNF- α , perforin, granzyme B, and FasL from PBMCs within 24 hours of disease onset. Control serum samples were obtained from patients taking the culprit medication without any adverse reaction. They found increased expression of TNF- α , granzyme B, perforin, and FasL in SJS and TEN patients compared with controls. TNF- α is known to activate T cells, and therefore the presence of elevated cytotoxic markers reflects activation of cytotoxic T cells.

Although Posades et al¹⁹ found evidence of activation of both cytotoxic pathways in TEN, other researchers noted a predominantly granule-mediated mechanism. Nassif et al¹⁸ analyzed blister fluid from a patient with TEN caused by trimethoprim-sulfamethoxazole and found that activated cytotoxic T cells were the predominant lymphocyte population (CD8⁺, CD3⁺, CD56⁺, CLA⁺). Using chromium-release assays, they reported no cytotoxicity of blister fluid cells toward an autologous Epstein-Barr virus-derived B-cell line. However, in the presence of cotrimoxazole, a dose-dependent cytotoxic effect was observed without prestimulation. Anti major histocompatibility complex class I mAb abolished the cytotoxicity as did concanamycin A, an inhibitor of perforin and granzyme. Anti-Fas did not abrogate the cytotoxicity. When taken together, these results indicate that drug-specific major histocompatibility complex class I restricted lymphocytes mediated their cytotoxic effect through perforin and granzyme B and not FasL. However, they demonstrated cytotoxicity to B cells and not to keratinocytes. A larger study by the same authors³⁰ demonstrated that cultured keratinocytes from TEN patients were lysed by autologous blister fluid in the presence of the culprit drug. These findings challenge the concept of FasL-mediated apoptosis in TEN.

Understanding the pathophysiology of disease constitutes the foundation for disease-specific treatments. Based on the

aforementioned information, trials were performed using IVIG to inhibit Fas-FasL interaction and cyclosporine to inhibit CD8 activation.

RECENT THERAPIES

Intravenous Immunoglobulin

As previously mentioned, Viard et al¹⁶ demonstrated that TEN epidermal cytotoxicity of Jurkat cells was attenuated by incubation with FasL blocking mAb. The IVIG preparations come from a large pool of healthy donors and therefore contain a wide variety of antibodies, some of which may be directed against FasL. When rhsFasL was incubated with IVIG before exposure to keratinocytes, no inhibition of lytic activity was noted. However, keratinocytes incubated with IVIG before adding rhsFasL inhibited apoptosis. Depletion of anti-Fas antibody from the IVIG preparation resulted in loss of its inhibitory effect, verifying that the inhibitory activity of IVIG is due to anti-Fas content. The authors treated 10 patients with TEN using IVIG in daily doses ranging from 0.2 to 0.75 g/kg daily for 4 consecutive days in an open, uncontrolled trial. They reported interruption of skin disease progression within 24 to 48 hours and rapid skin healing within 4 to 12 days (mean, 6.9 days) in all patients. The findings spurred a number of case reports, virtually all of which showed favorable results with IVIG.^{31–38} Since 1998, the use of IVIG in TEN has been increasing, in part due to the absence of effective alternative therapies.

The enthusiasm for IVIG may be tempered by the fact that the study by Viard et al¹⁶ was open and involved a small number of patients. Some studies have even suggested that IVIG may have proapoptotic activity.^{39,40} The extremely low prevalence of TEN renders randomized controlled trials on a large number of patients difficult and costly to perform. It is estimated that a controlled trial would need to enroll more than 1,000 patients to demonstrate a mortality decrease from 21% to 17%.⁴¹ Nevertheless, data from a number of case series have added to our understanding of the effectiveness of IVIG in TEN.

Studies in Support of IVIG Therapy

Trent et al⁴² conducted a retrospective analysis of 16 patients with biopsy-confirmed TEN treated with IVIG in addition to a standard TEN therapy protocol. Mortality was the main outcome measure and was compared with an expected mortality using a validated predictor (score for the evaluation of toxic epidermal necrolysis [SCORTEN]) (Table 2).⁴³ A standardized mortality ratio analysis was used to evaluate the effectiveness of IVIG. All patients received 1 g/kg daily of IVIG for 4 consecutive days, except 1 patient who was undergoing dialysis, who received 0.4 g/kg daily. Whereas the expected mortality was 36.3% (5.81 patients), the actual mortality was limited to 1 patient (6.25%). Such a difference represented an 83% mortality reduction.

Prins et al⁴⁴ conducted a multicenter, uncontrolled, retrospective analysis of 48 patients with TEN (43 confirmed by histologic analysis) treated for 1 to 5 days (mean, 4 days)

Table 2. Score for the Evaluation of Toxic Epidermal Necrolysis (SCORTEN) for Assessment and Predicting Mortality*

Age >40 y
Presence of malignancy
Heart rate >120/min
Body surface area involved >10%
Serum urea >10 mmol/L (28 mg/dL)
Serum glucose >14 mmol/L (252 mg/dL)
Serum bicarbonate <20 mmol/L (20 mEq/L)

* Adapted from Bastuji-Garin et al.⁴⁴ One point assigned for each risk factor. Expected mortality based on total score: 0 to 1 (3.2%), 2 (12.1%), 3 (35.3%), 4 (58.3%), or 5 or more (90%).

with a mean total IVIG dose of 2.7 g/kg (range, 0.65–5.8 g/kg) (Table 3). The final outcome at day 45 revealed a 12% mortality. Lack of response to IVIG was associated with older age, greater surface of epidermal detachment, concomitant disease, delay in time to IVIG administration, and lower mean dose of IVIG. Interestingly, 11 (26%) of the survivors received systemic corticosteroids before IVIG, compared with 1 (17%) of the 6 deaths. This difference, however, was not statistically significant. Trials of IVIG limited to children with SJS and TEN demonstrated both efficacy and safety^{45–48} (Table 3).

Studies Not in Support of IVIG Therapy

Bachot et al⁴¹ conducted a prospective, open trial of 34 consecutive patients with biopsy-confirmed SJS (n = 9), TEN (n = 20), and overlap (n = 5), including 12 patients (35%) with acquired immunodeficiency syndrome (AIDS). Patients were admitted 1 to 9 days (mean, 4.1 days) after onset of symptoms. They were treated within 2 days of admission (not onset) with a one-time dose of 2 g/kg of IVIG except in 3 patients who received 1 g/kg. The main outcome measures were the extent of epidermal detachment and mortality compared with SCORTEN-predicted death rate. The observed mortality of 11 deaths (32%) was higher than the predicted (8.2 deaths; 24%), with the excess mortality mainly in elderly patients (70 years or older). At day 3, epidermal detachment progressed in 22, remained unchanged in 7, and regressed in 4 patients.

The authors contemplated whether delayed therapy was a factor. However, they noted that earlier hospitalization (within 4 days of onset) was associated with more progression of epidermal detachment. The patients received an average total IVIG dose of 1.9 g/kg, which was associated with a poor prognosis in the study by Prins et al. However, other researchers have reported beneficial effects of IVIG at or below that dose^{49,50} (Table 3). The significant number of patients with AIDS in the study by Bachot et al may have contributed to the high mortality, although presumably this is accounted for by using SCORTEN. However, it can be argued that AIDS may have a unique effect on the progression of epidermal destruction. In fact, 11 (50%) of the 22 progressors had AIDS, whereas AIDS-affected patients only comprised 35% of the entire study group. The authors postulated

Table 3. Summary of Studies of IVIG in SJS and TEN

Source, y	No. of patients	Age, mean (range) or mean $\pm$ SD, y	Diagnosis	BSA epidermal sloughing, mean (range) or mean $\pm$ SD, %	Time to IVIG, mean (range) or mean $\pm$ SD, d	Mean total IVIG dose, g/kg*	Time to arrest progression, mean (range), d	Time to complete skin healing, mean (range) or mean $\pm$ SD, d	Deaths, %
Studies in support of IVIG									
Viard et al, 1998	10	39.4 (11–88)	SJ/OL/TEN	28.5 (5–60)	3.6 (2–5)	2.5	1.5 (1–2)	6.9 (4–12)	0
Stella et al, 2001	9	54.0 (27–68)	SJ/OL/TEN	16.4 (4–37)	6.1 (1–15)	2.8	4.8 (3–10)	12.125 (7–17)	1 (11)
Prins et al, 2003	48	43 (4–95)	OL/TEN	44.8 (10–95)	7.3 (2–30)	2.7	2.3 (1–6)	15 (4–40)	6 (12)
Campione et al, 2003	10	48.6 (20–95)	OL/TEN	48.5 (15–80)	≤ 3	2	NR	(25–40)	1 (10)
Trent et al, 2003	16	42.8 (19–62)	OL/TEN	>42 (12–>90)	3.5	3.9	3.75 (1–17)	8.5 (4–23)	1 (6.25)
Prins et al, 2003	12	44 (8–88)	SJS	6 (0–10)	4.25 (1–10)	2.4	2.0 (1–3)	9.0 (4–18)	0
Al-Mutairi et al, 2004	12	27.2 (7–50)	TEN	57.5 (30–90)	1.58 (1–3)	3.4	2.83 (1–5)	7.33 (5–13)	0
Tan et al, 2005	12	49.9 (19–70)	OL/TEN	NR	8.7 (3–22)	1.75	3.6 (2–8)	NR	1 (8.4)
Studies in support of IVIG in children									
Morici et al, 2000	6	7.5 (4–13)	SJS	NR	3 (1–8)	1.9	NR	NR	0
Tristani-Firouzi et al, 2002	8	8.1 (22 m–21)	TEN	67 (30–90)	3.25 (2–5)	2.4	2.1 (1–4)	8.1 (3–14)	0
Metry et al, 2003	7	9.8 (3–15)	SJS	NR	2.7 (1–6)	2.0	2.3 (1–3)	NR	0
Kanu et al, 2005	10	2.7 (6 m–12)	TEN	66.7 (45–81)	3.1 (2–4)	0.25–0.5	2.1 (1.8–2.5)	8.3 (5.4–10.7)	0
Studies not in support of IVIG									
Banchot et al, 2003	34	47 (13–88)	SJ/OL/TEN	19 (1–62)	4.1 (1–9)	1.9	NR	18 (3–75)	11 (32)
Shortt et al, 2004	16	53 $\pm$ 21	OL/TEN	35 $\pm$ 26	4.5 $\pm$ 2.7	3.0	NR	11.2 $\pm$ 3.6	4/16 (25)
Brown et al, 2004	24	47 $\pm$ 21	OL/TEN	44.9 $\pm$ 24.6	9.2 $\pm$ 1.2	1.6	NR	17.8 $\pm$ 10.3	10/24 (41.7)

Abbreviations: BSA, body surface area; IVIG, intravenous immunoglobulin; NR, not reported; OL, overlap syndrome; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

* Daily dose varied between 0.2 and 2.9 mg/kg for adults and 0.05 to 2.0 mg/kg for children. Treatment duration varied from 1 to 8 days in adults and 1 to 7 days in children.

that multiple apoptotic pathways are likely involved in TEN and thus blocking one pathway is not effective.

Shortt et al⁵¹ performed a retrospective cohort review of 32 TEN and overlap cases; 16 received a mean daily dose of IVIG of 0.7 g/kg (range, 0.5–1.4 g/kg) for a mean of 4 days (range, 2–8 days) compared with 16 historical controls who did not receive IVIG. Outcomes included mortality, progression of skin lesions, and other markers of illness severity. Both groups were found to be well matched except for a significantly longer delay to admission in the control group (9.1 vs 4.8 days). Although the investigators reported no statistically significant differences in any of the outcomes, there were 2 fewer deaths in the treated group (4 vs 6). It is worth noting, however, that the lower mortality in the IVIG group may be partly attributable to earlier treatment. In addition to being retrospective, this study is limited by its small sample size (16 in each group). Interestingly, the authors of that study stated that “we continue to use IVIG for patients with TEN.”

Brown et al⁵² conducted a retrospective review of 24 TEN patients treated with IVIG (400 mg/kg daily for 4 days) and compared the results to a historical control group of 21 patients. The outcomes included mortality and several markers of disease severity. The average SCORTEN between the 2 groups was similar, yet the overall mortality was higher in the IVIG group than in the control group (41.7% vs 28.6%), but this difference was not statistically significant. Also, the number of complications per patient throughout hospitalization was significantly higher in the IVIG group (2.8 vs 1.7 per patient). However, there was a trend toward a greater delay to admission in the IVIG group that may confound the observed effects in such a small group and could at least partly explain both the greater number of complications and high mortality in the IVIG group.

Regarding the reported adverse events with IVIG therapy, they were generally rare and self-limited and include headache, nausea, and gastrointestinal tract disturbances.⁴⁹ Nephrotoxicity was rare and occurred primarily in patients with compromised renal function treated with high doses, particularly with high-osmolality preparations.⁴¹ Thromboembolic events are more likely to occur with high doses in elderly patients.⁵³

IVIG Therapy Outcome Comparisons

Reviewing these studies and others^{54–56} (Table 3) revealed marked differences in study design, sample size, age, time to admission, severity of disease, comorbid conditions, and IVIG used. The latter comprises the dose, duration, and preparation. Of great significance is the variability in the anti-Fas antibody content from batch to batch.⁴⁴ For example, in the study by Bachot et al, 30 of the 34 patients received a single brand of IVIG. Perhaps their negative results may be in part due to a possible low content of anti-Fas antibody in that particular preparation.

Studies that support IVIG therapy in adults used a mean total dose of 1.75 to 3.9 g/kg, and studies that showed no

beneficial effect used a similar mean dose of 1.6 to 3 g/kg. The lowest dose (1.6 g/kg) was used by Brown et al, which might be a factor in that study's unfavorable outcome. Although in one study⁴⁴ poorer outcome was associated with lower total dose of IVIG (2 g/kg), other studies reported improved outcomes with IVIG at or below that dose.^{49,50} Therefore, although it seems unlikely that the total dose accounts for the different results, an optimal dose remains to be determined.

An association between a worse outcome and delay in initiating treatment was observed in one study,⁴⁴ but not in others.^{41,51} Also, an association between increased BSA involvement and mortality was reported in one study,⁴⁴ but not in others.^{46,56} The wide variation in patient ages may account for some of the differences; advanced age was associated with worse outcomes in some studies,^{41,44,57} although this was not noted in another.⁵²

Although comparing mortality data based on compilation of widely disparate and uncontrolled studies is not scientifically optimal, mortality was 0% to 12% in studies that supported the use of IVIG and 25% to 41.7% in those that did not demonstrate a beneficial effect. Such a discrepancy may be partly attributed to the inclusion of more patients with SJS in the studies that support the use of IVIG. For example, in the series of patients studied by Viard et al¹⁶ who were considered to have TEN, 5 of the 10 patients would currently be classified as having SJS or overlap and would be expected to have a markedly lower mortality rate. Furthermore, the conclusions of some studies were based on comparisons with historical (retrospective) control groups that were very likely to have received different supportive and medical care.^{46,51,52} Hence, the observed beneficial effects of IVIG may be overestimated.

Cyclosporine

In addition to its antiapoptotic activity, one of the immunosuppressant mechanisms of cyclosporine is inhibition of CD8 activation.⁵⁸ Theoretically, this will inhibit downstream cytotoxic epidermal apoptosis and destruction through either FasL or the perforin-granzyme pathway.⁵⁹ The literature on cyclosporine therapy in TEN is not as robust as for IVIG. To the best of our knowledge, the number of described patients treated with cyclosporine totaled 23 with doses of 3 to 10 mg/kg daily (Table 4).^{60–68} Although it would be difficult to make a solid conclusion based on case reports, the outcome was consistently favorable. The series of Arévalo et al⁶⁹ was composed of 11 patients with TEN, involving 35% to 96% of BSA (median, 90%) who were treated with 3 mg/kg daily of cyclosporine during a 4-week tapering course. They were compared with a historical group that was treated with cyclophosphamide and steroids and were comparable in age, BSA involvement, and time to admission. They found that use of cyclosporine was associated with a significant improvement in time to disease arrest, complete reepithelialization, and survival, without significant adverse events.

Table 4. Summary of Studies of Cyclosporine Therapy in Toxic Epidermal Necrolysis*

Source, y	No. of patients	Age, y	BSA, %	Cyclosporine dose, mg/kg daily	Duration of cyclosporine therapy, d	Time to arrest progression, h	Time to reepithelialization, d
Renfro et al, 1989	1	35	NR	4	8	5	>10
Hewitt et al, 1992	2	34/37	>35/40	3.6/3	10/9	36/24	NR/NR
Zaki et al, 1995	1	34	>65	4	25	48	NR
Sullivan et al, 1996	1	29	50	4.5	16	24	14
Jarrett et al, 1997	1	42	80	4	15	24	15
Jarrett et al, 1997	1	49	50–60	5	12	Within hours	12
Szepietowski et al, 1997	3	60	50–60	10	10	36	12–14
		48	70	10	10	48	17
		8	100	8	21	NR	28
Arevalo et al, 2000	11	42 (29–82)*	83 (35–96)*	6	>28	34 (24–48)*	12 (6–18)*
Robak et al, 2001	1	23	50	500 mg/d	NR	72	7
Yung et al, 2002	1	27	40	4	NR	24	NR

Abbreviations: BSA, body surface area; NR, not reported.

* Data presented as mean (range).

Paquet et al⁷⁰ explored the laboratory and clinical effects of IVIG and cyclosporine. Using standard histologic and immunohistochemical analysis, they examined skin biopsy specimens from involved and uninvolved areas from 6 patients with TEN at admission (before therapy) and after 5 days of treatment with IVIG (0.75 g/kg daily) (n = 2), cyclosporine (5 mg/kg daily) (n = 2), or supportive care only (n = 2). At day 5 there were no differences in macrophage, T lymphocyte, and dendrocyte densities among the 3 groups. However, epidermal Fas receptor expression decreased in the involved skin of the 2 treatment groups, whereas it increased in the group that received supportive care only. Clinically, however, this did not translate into a more rapid rate of reepithelialization. In summary, both cyclosporine and IVIG decreased the expression of Fas receptor but did not reverse the clinical evolution of disease in this small study. Interestingly, cyclosporine did not down-regulate activated T lymphocytes, suggesting that cyclosporine inhibits activation of CD8 lymphocytes but does not inhibit the cytotoxicity of previously activated cells.

CONCLUSION

Our understanding of the pathophysiology of SJS and TEN has markedly improved during the last decade. Epidermal death and sloughing are caused by apoptosis that has been attributed to a few mechanisms, particularly Fas-FasL interaction and CD8 cell cytotoxicity. Advancement in laboratory medicine has enhanced the development of new therapies. For many years, treatment of TEN was primarily supportive care. Recently, treatments aimed at inhibiting specific targets such as Fas death receptor and CD8 cytotoxic T cells have been introduced. Both IVIG and cyclosporine have been used with varying degrees of success. IVIG contains anti-Fas antibodies that can block Fas-FasL interactions. As an immunosuppressant, cyclosporine inhibits cytotoxic T cells. Because of the relative rarity of SJS and TEN, reports on the use

of these 2 therapies, particularly for cyclosporine, are relatively few and not optimally comparable. The available information, in general, indicates that such therapeutic modalities were associated with enhanced healing and better survival. The lack of benefit or increased adverse events that have been reported in some studies should not abrogate the benefit noted in most published studies, especially in a disease with high mortality and limited therapeutic options. It is worth noting that the studies differed in several critical aspects, particularly study design and patient populations. Further studies are certainly needed and ideally should be multicenter, randomized, double-blind, and placebo-controlled, with standardized classification of disease severity, preset primary and secondary outcomes, and standardized therapy regarding dose, duration, and preparations. Further studies are expected to enhance our understanding of the pathogenesis of SJS and TEN with consequent improvement in the treatments and ultimate outcome.

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Objectives: After reading this article, participants should be able to demonstrate an increased understanding of their knowledge of allergy/asthma/immunology clinical treatment and how this new information can be applied to their own practices.

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CME Examination

1–5, Khalili B and Bahna SL. 2006;97:272–281.

CME Test Questions

1. All of the following statements regarding toxic epidermal necrolysis (TEN) are true *except*:
 - a. Biopsy specimens typically show full-thickness epidermal necrosis.
 - b. Systemic corticosteroid use is controversial.
 - c. Mortality has not been substantially improved in part due to lack of specific therapies.
 - d. Epidermal sloughing is due to keratinocyte necrosis.
 - e. Cytotoxic T cells can cause apoptosis in either caspase-dependent or caspase-independent mechanisms.
2. The score for the evaluation of toxic epidermal necrolysis (SCORTEN) include all the following *except*:
 - a. heart rate
 - b. sex
 - c. percentage of body surface area involved
 - d. serum glucose
 - e. age
3. Which of the following statements about TEN is *not true*?
 - a. Serum from patients with TEN expressed elevated soluble Fas ligand (sFasL).
 - b. Skin sections from patients with TEN expressed FasL.
 - c. FasL on keratinocytes were lytically active.
4. Which of the following is true regarding the use of cyclosporine in TEN?
 - a. It is supported by randomized, placebo-controlled trials.
 - b. Typical doses used are 10 to 20 mg/kg daily.
 - c. Cyclosporine does not appear to down-regulate already activated T lymphocytes.
 - d. Reported mortality is high.
 - e. Cyclosporine is associated with improvement in disease arrest but does not shorten the time to complete reepithelialization.
5. All of the following are true about the role of interferon- γ in TEN *except*:
 - a. It causes keratinocyte activation.
 - b. It increases levels of sFasL.
 - c. It directly causes keratinocyte apoptosis.
 - d. It increases levels of tumor necrosis factor α .
 - e. Elevated concentrations appear in blister fluid.

Answers on page 320.