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REVIEW ARTICLE

Toxic Epidermal Necrolysis and Stevens Johnson Syndrome: Our Current Understanding

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ABSTRACT

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN, Lyell's syndrome) are now considered to be distinct clinical entities within a spectrum of adverse cutaneous drug reactions of increasing severity based on their surface of skin detachment. Within this spectrum, SJS which can be considered as a minor form of TEN is characterized by less than 10% body surface area of skin detachment, and an average reported mortality of 1−5%, whereas TEN is characterized by more than 30% skin detachment, and an average reported mortality 25−35%.

Both SJS and TEN are characterized morphologically by the rapid onset of keratinocyte cell death by apoptosis, a process that results in the separation of the epidermis from the dermis. Recent evidence is supportive of a role for inflammatory cytokines and the death receptor Fas and its ligand FasL in the pathogenesis of keratinocyte apoptosis during TEN. This Fas-mediated keratinocyte apoptosis that is the last step culminating in epidermal detachment in TEN can be inhibited *in vitro* by antagonistic monoclonal antibodies to Fas, and by intravenous immunoglobulins (IVIG) which have been shown to contain natural anti-Fas antibodies.

Consequently, over the last few years, numerous case reports and 9 non-controlled clinical studies containing 10 or more patients have analyzed the therapeutic effect of IVIG in TEN. Taken together, although each study has its potential biases, 7 of 9 such studies point towards a benefit of IVIG used at doses greater than 2 g/kg on the mortality associated with TEN. These studies should serve as the basis for designing an appropriate prospective trial or for conducting a metaanalysis in the near future, in order to determine the therapeutic efficacy of IVIG in TEN.

KEY WORDS

apoptosis, Fas, intravenous immunoglobulin, Lyell's syndrome, Severe adverse drug reaction

INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe adverse drug reactions characterized by a low incidence but high mortality. The incidence of SJS is approximately 6 cases per million persons per year, and that of TEN is approximately 2 cases per million persons per year.[1]

Historically, SJS was first described in 1922 by two American physicians named Stevens and Johnson. They described an acute mucocutaneous syndrome in two young boys characterized by severe purulent conjunctivitis, severe stomatitis with extensive mucosal necrosis, and 'Erythema multiforme-like' cutaneous lesions.It became known as Stevens-Johnson syndrome (SJS) and was recognized as a severe mucocutaneous disease with a prolonged course and occasional fatalities, and is now known to ba an adverse drug reaction and clinically distinct from erythema multiforme major which is in most cases parainfectious.[2-4] TEN, also called Lyell's syndrome was first described by the scottish dermatologist Alan Lyell in 1956. He reported four patients with an eruption 'resembling scalding of the skin objectively and subjectively', which he called toxic epidermal necrolysis or TEN.[5] 'Toxic' referred to toxemia-circulation of a toxin-which was thought at the time to be responsible for the constitutional symptoms and epidermal

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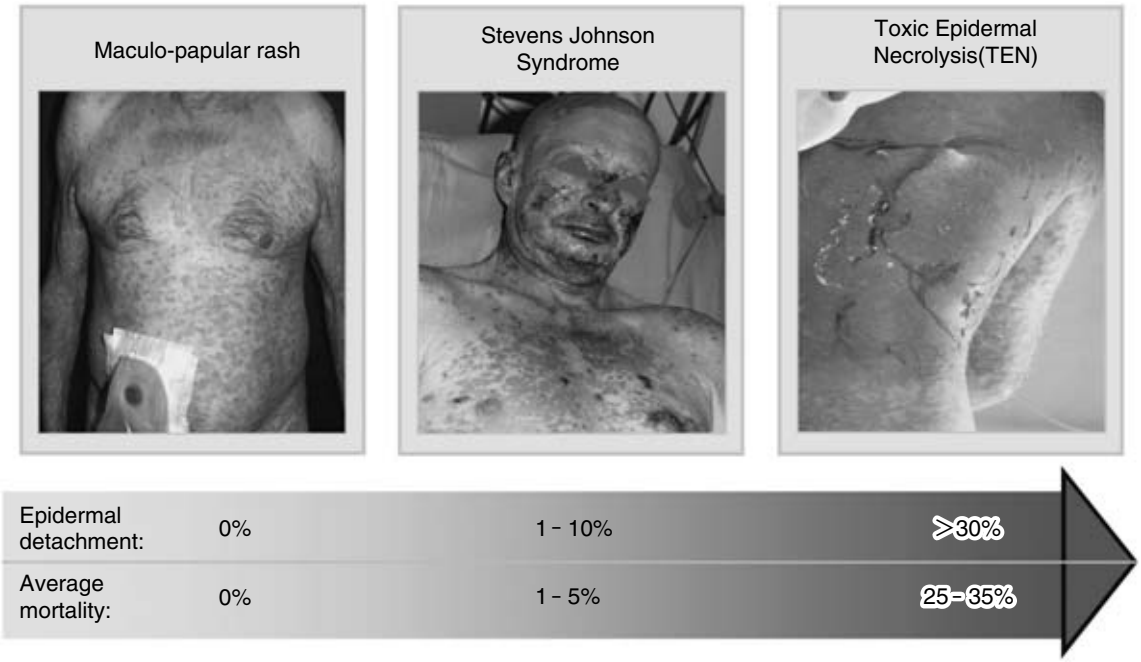

Fig. 1 The spectrum of adverse drug reactions of increasing severity ranging from the benign maculo-papular rash to SJS, and TEN

necrosis. Lyell coined the term 'necrolysis', by combining the key clinical feature 'epidermolysis' with the characteristic histopathological feature 'necrosis'. He also described an attack on the mucous membranes as part of the syndrome, and noted that there was very little inflammation in the dermis, a feature that was later referred to as 'dermal silence'.[6] This feature contrasted with the obvious inflammatory infiltrate of other blistering disorders such as erythema multiforme, dermatitis herpetiformis, and bullous pemphigoid. Although the origin of the 'toxin' was not immediately obvious, it is now well established that an adverse reaction to certain drugs is the cause of TEN.

CLINICAL FEATURES OF STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

SJS and TEN are idiosyncratic in nature and thereby have the potential to affect any individual taking a medication, the most frequently incriminated drugs being antibiotics, non-steroidal anti-inflammatory drugs and anti-convulsants. SJS and TEN are currently considered to be part of a spectrum of clinically and pathogenically related drug-induced skin diseases with increasing severity (Fig. 1). In contrast to the common morbiliform drug rash that is not associated with epidermal detachment, both SJS and TEN are characterized by epidermal detachment ranging from mild (1–10% of total body surface area (TBSA) in SJS), to moderate (10–30% TBSA) in what Bastuji-Garin *et al.* refer to as SJS-TEN overlap,[3] and severe (>30% TBSA) in full-blown TEN (Fig. 1). Within this spectrum, the severity or extent of epidermal detachment is tightly correlated with the observed rate of mortality, the latter ranging from 1–5% in SJS to 25–35% in TEN according to the epidemiological studies puiblished in the litterature over the past decade.[1,7,8]

With the objective of being able to precisely predict patient mortality, Batuji-Garin *et al.* have recently proposed a scoring system for TEN named the SCORTEN severity of illness score (Fig. 2).[9] Seven clinico-biologic parameters including known adverse prognostic factors such as age greater than 40-years and initial surface of epidermal detachment greater than 10%, are given one point if positive and zero if negative. Computing the sum of the scores for each clinico-biologic parameter results in a "SCORTEN" ranging from 0 to 7, with a score of 0 or 1 predicting a mortality of 3.2%, and a score of 5 or above predicting a mortality of greater than 90%. This scoring system that was developped with a french-based patient cohort has recently been validated in a US-based patient cohort,[10] and is proving to be a valuable tool for predicting patient outcome.

Initial symptoms of both TEN and SJS can be fever, stinging eyes, and pain upon swallowing, any of which can precede cutaneous manifestations by 1 to 3 days. Skin lesions tend to appear first on the trunk, spreading to the neck, face, and proximal upper extremities. The distal portions of the arms as well the legs are relatively spared, but the palms and soles can

CLINICAL-BIOLOGIC PARAMETER	INDIVIDUAL SCORE	SCORTEN (sum of individual scores)	PREDICTED MORTALITY (%)
Age > 40y	yes = 1, No = 0	0−1	3.2
Malignancy	yes = 1, No = 0	2	12.1
Tachycardia (> 120/min)	yes = 1, No = 0	3	35.3
Initial surface of epidermal detachment > 10%	yes = 1, No = 0	4	58.3
Serum urea > 10 mmol/L	yes = 1, No = 0	≥ 5	90
Serum glucose > 14 mmol/L	yes = 1, No = 0		
Bicarbonate < 20 mmol/L	yes = 1, No = 0		

Fig. 2 The SCORTEN clinical scoring system for predicting outcome in TEN

be an early site of involvement. Erythema and erosions of the buccal, ocular, and genital mucosa are present in more than 90% of patients. The epithelium of the respiratory tract is involved in 25% of cases of TEN, and gastrointestinal lesions can also occur. The skin lesions are usually tender, and mucosal erosions are very painful. The morphology of the skin lesions has been studied in detail. First, lesions appear as erythematous, dusky-red, or purpuric macules of irregular size and shape, and have a tendency to coalesce. At this stage, and in the presence of mucosal involvement and tenderness, the risk of rapid progression to SJS or TEN should be strongly suspected. As the epidermal involvement progresses toward full-thickness necrosis, the dusky-red macular lesions take on a characteristic gray hue. This process can be very rapid (hours), or take several days. The necrotic epidermis then detaches from the underlying dermis, and fluid fills the space between the dermis and the epidermis, giving rise to blisters. The blisters have special features: they break easily (flaccid) and can be extended sideways by slight pressure of the thumb as more necrotic epidermis is displaced laterally (Nikolsky sign). The skin resembles wet cigarette paper as it is pulled away by trauma, often revealing large areas of raw and bleeding dermis.

EPIDEMIOLOGY

SJS and TEN are rare diseases with an annual incidence of 1.2−6 and 0.4−1.2 per million persons, respectively. TEN affects women more frequently than men with a ratio of 1.5 : 1, and the incidence increases with age.[11] Patient groups particularly at risk are those with slow acetylator genotypes, immunocompromised patients (e.g. HIV infection, lymphoma), and patients with brain tumors who are undergoing radiotherapy and concomitantly receiving antiepileptics.[12,13]

Use of therapeutic drugs is reported in over 95% of patients with TEN. A strong association between drug ingestion and development of the cutaneous eruption is observed in 80% of cases. Other rare causes include infections and immunizations. The literature reflects a less clear relationship between drugs and SJS, as only 50% of reported SJS cases are claimed to be drug related. This is certainly an underestimation, however, and most likely is due, in part, to the confusion that previously existed concerning the diagnostic distinction between SJS and erythema multiforme.

More than 100 drugs have been identified to date as being associated with SJS/TEN. The most frequently implicated drugs consist primarily of antibiotics, NSAIDs, and anticonvulsants. Among the former, sulfonamides are the most strongly associated with SJS/TEN; other antibiotics include aminopenicillins, quinolones, cephalosporins, tetracyclines, and imidazole antifungals. For these drugs, the risk of developing SJS/TEN is reported to be highest during the initial week (s) of therapy. For the aromatic anticonvulsants, the risk is highest during the first 2 months of treatment.[14] Furthermore, drugs with long half-lives are more likely to cause drug reactions and a fatal outcome than those with short half-lives, even if they are chemically related.[15]

PATHOGENESIS

To date, the precise sequence of molecular and cellular events that lead to the development of SJS/TEN is only partially understood. The proposed pathogenesis has to take into account the rarity of these diseases and the involvement of specific types of drugs.

Circumstantial evidence suggests that SJS/TEN is associated with an impaired capacity to detoxify reactive intermediate drug metabolites. It is thought to be initiated by an immune response to an antigenic complex formed by the reaction of such metabolites with certain host tissues.[16-20] Genetic susceptibility may also play a role, as evidenced by the increased incidence of HLA-B12 in individuals affected by TEN.[21] In SJS and TEN due to allopurinol, a genetic predisposition in Han Chinese with the HLA-B*5801 allele has recently been identified.[22] Furthermore, a strong association between HLA-B*1502, and Stevens-Johnson syndrome induced by carbamazepine was also reported in the Han Chinese population.[23]

Cytotoxic T cells expressing the skin-homing receptor, cutaneous lymphocyte-associated antigen

(CLA), are seen early in the development of cutaneous lesions.[24-26] These are likely to be drug-specific cytotoxic T cells.[27,28] Important cytokines such as interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), interferon gamma, interleukin 18 (IL-18), and Fas ligand (FasL) are also present in the lesional epidermis and or blister fluid of patients with TEN, and their actions could explain some of the constitutional symptoms of TEN as well as the frequently observed discrepancy between the extent of epidermal damage and the paucity of the inflammatory infiltrate.[29] Lastly, the typical interval between the onset of drug therapy and SJS/TEN is between 1 and 3 weeks, suggesting a period of sensitization and providing further support for the role of the immune system in the pathogenesis of SJS/TEN. This period ('memory') is considerably shortened in patients who are unfortunately re-exposed to a drug that previously resulted in SJS or TEN.

Recently, it has been clearly shown that the tissue damage described by pathologists as epidermal necrolysis is due to massive keratinocyte cell death via apoptosis.[30] Keratinocyte apoptosis is clearly a hallmark of the early stages of SJS and TEN, and it is the first clear morphological sign of tissue damage in this disease. The more classic histologic image of extensive epidermal 'necrolysis' is in fact an image of the aftermath of keratinocyte apoptosis, since the apoptotic state of cells is known to be transient in nature.

Recent advances in our understanding of the molecular control of apoptosis have provided insights into a possible triggering mechanism for the massive keratinocyte apoptosis that characterizes TEN and probably also SJS. Certain cytokines of the TNF family, by binding to their specific cell-surface receptors (death receptors), have the ability to induce apoptosis.[31] We and others have recently shown that keratinocyte apoptosis in lesional skin of patients with TEN is associated with highly increased expression of keratinocyte membrane-bound FasL, together with conserved levels of keratinocyte Fas expression.[29,32,33] Functional experiments, performed by overlaying cryostat sections of lesional skin with Fas-sensitive cells as targets, have further demonstrated that keratinocyte FasL is cytolytically active in TEN. This cytolytic activity can be blocked with monoclonal antibodies that interfere with the interaction of Fas and FasL, thus supporting the hypothesis that increased keratinocyte FasL expression is responsible for the keratinocyte apoptosis that characterizes TEN.

The emerging model as shown in Figure 3 is that, in normal skin, low levels of FasL are expressed by keratinocytes and localized intracellularly.[34] In lesional skin of TEN, high levels of FasL are expressed by keratinocytes and localized at the cell surface. As a result, cell surface interactions between keratinocyte Fas and FasL on adjacent cells are then possible.

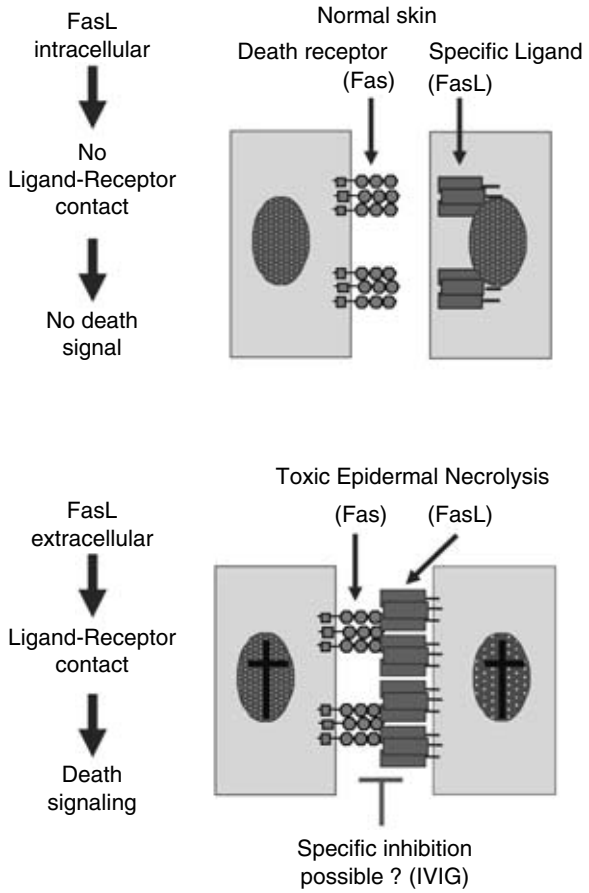

Fig. 3 Fas-mediated keratinocyte apoptosis in TEN and potential mechanism of inhibition by IVIG for example. Top panel, normal epidermis: weak FasL expression and intracellular localisation prevent binding to Fas and triggering of keratinocyte apoptosis; bottom panel, Toxic epidermal necrolysis: Induction of keratinocyte FasL expression and interaction with Fas at the cell surface, leading to keratinocyte apoptosis.

Upon contact with Fas, cell surface FasL induces Fas multimerization and rapid signaling of keratinocyte cell death by apoptosis. As Fas and FasL are co-expressed on a large number of keratinocytes in lesional skin, keratinocyte apoptosis can be abundant, resulting in the destruction of large areas of epidermis. This recent concept of the pathogenesis of TEN provides new potential avenues for therapeutic intervention.

TREATMENT

Optimal medical management of SJS and TEN requires early diagnosis, immediate discontinuation of the causative drug(s), supportive care, and specific therapy. Attempts have been made to decrease mortality in TEN patients essentially through improved supportive care. The low prevalence of TEN makes

Author	Viard Science 1998	Prins Arch Derm 2003	Trent Arch Derm 2003	Bachot Arch Derm 2003	Campione Acta Derm 2003	Shortt J Burn Care 2003	Brown J Burn Care 2004	Al-Mutairi Int J Derm 2004	Tan J Dermatol 2005
Study	Prosp Non-cont	Retrosp Non-cont	Retrosp Non-cont	Prosp Non-cont	Prosp Non-cont	Retrosp Non-cont	Retrosp Non-cont	Prosp Non-cont	Retrosp Non-cont
Patients	10	48	16	34	10	32	45	12	12
Age	39	43	43	47	49	53	45	27	50
Detachment	28.5	45	43	19	49	65 (rash)	49	58	NR
Dose IVIG	3 g/kg	3 g/kg	4 g/kg	2 g/kg	2 g/kg	2.8 g/kg	1.6 g/kg	2−5 g/kg	2 g/kg
Predicted deaths	-----	-----	5.8 (36%)	8.2 (24%)	3.5 (35%)	6 (38%)	6 (28.6%)	-----	-----
Actual deaths	0/10 (0%)	6/48 (12%)	1/16 (6%)	11 (32%)	1 (10%)	4 (25%)	10 (41.7%)	0 (0%)	1 (8%)

Fig. 4 Summary of studies reporting the effect of IVIG in more than 10 patients. NR: not reported.

randomized clinical trials hard to perform however, and consequently most reported therapeutic approaches consist of individual cases or small uncontrolled series. In such studies, several treatments, including cyclosporine (ciclosporin; 3−4 mg/kg/day), cyclophosphamide (100−300 mg/day), plasmapheresis, and N-acetylcysteine (2 g/6hr) have shown promising results.[35-40] The use of systemic corticosteroids remains controversial, and it may even increase mortality.Recently, a controlled study using thalidomide was interrupted because of higher mortality in the thalidomide group (10 of 12 patients died) compared with the placebo group (3 of 10 patients died).[41] It was suggested that the increased mortality may have been due to a paradoxical increase in TNF-alpha production.

In theory, and based on recent research, therapies that have the potential to selectively block keratinocyte apoptosis have significant potential for treating TEN. In 1998, we reported that commercial preparations of intravenous immunoglobulins (IVIG) contain antibodies against Fas that are able to block the binding of FasL to Fas.[32] Furthermore intravenous immunoglobulins, by blocking Fas, potently inhibit cell death mediated by recombinant FasL *in vitro*. In the same report, we suggested based on the results of a pilot trial, that IVIG used in high doses (0.75 g/kg/day for 4 consecutive days) to treat patients with TEN, consistently and rapidly blocked the progression of skin detachment and disease in 10 out of 10 patients.[32] Since then, 8 other reports of studies with 10 or more patients treated with intravenous immunoglobulin (IVIG) for TEN have been published.[42-49] While none of these studies are controlled, and the results illustrate that controversy as to the efficacy of IVIG still exists, interesting information can be extracted from their analysis (Fig. 4).

The largest of the studies summarized in Figure 4 was a multicenter study of 48 patients with TEN treated with IVIG at a mean total dose of 2.7g/kg (doses ranging from 0.65−5.8 g/kg divided over 1−5 days) starting on average 7.3 days after the onset of disease.[42] Success was concluded based upon an 88% survival rate, but also the rapid (mean of 2.3 d) cessation of skin and mucosal detachment in 89.6% of patients. Mortality was associated with a lower dose of IVIG, longer time of onset to IVIG use, co-existing underlying chronic conditions, older age, and greater body surface area involved.

Two other studies published simultaneously by Trent *et al.* and Bachot *et al.*, used SCORTEN to compare the effect of IVIG on expected mortality and reported contradictory results.[43,44] Trent *et al.* analyzed in a retrospective non controlled manner 16 patients with a mean TBSA of epidermal detachment of 43%, and Bachot *et al.* studied in a prospective non controlled manner 34 patients with a mean TBSA of epidermal detachment of 19%. Whereas Trent *et al.* found an 84.4% reduction in predicted mortality in patients treated with IVIG, the Bachot study reported an increase in mortality (24% predicted *vs.* 32% observed). However, it is of note that the latter study included several SJS patients at admission, two of which were considered as TEN by day 3, thus possibly leading to a lower than predicted SCORTEN. Also, 32 of 34 patients in the Bachot study were treated with IVIG originating from the same batch, and we have reported that large batch to batch variability in anti-Fas activity can be observed in IVIG, with rare batches even completely lacking activity.[42] Finally, differences in doses of IVIG used in the two studies (2 g/kg in the Bachot study *vs.* 4 g/kg in the Trent study) may have contributed to the different outcomes.

The study by Campione *et al.* describes 10 patients suffering from TEN with a mean TBSA of 44% that were treated with 400 mg/kg of IVIG per day on 5 consecutive days (2 g/kg total dose), starting on average 3 days after disease onset.[45] According to the calculated SCORTEN for this patient cohort at admission, the predicted mortality rate was 35%, and the observed mortality after intravenous immunoglobulin

therapy was of 10%. The authors also report that in 9 of their patients, clinical improvement could already be observed after the first infusion of IVIG.

Shortt *et al.* report the results of a retrospective non-controlled analysis of 32 patients with TEN evaluated to have a mean TBSA of 65%, 16 of which recieved IVIG at a total dose of 2.8 g/kg and 16 others standard care only.[46] A mortality of 25% was observed in the IVIG-treated group against 38% in the standard care group. Although the authors correctly state that the observed difference in mortality is not significant (p= 0.364), significance may have been achieved had the study groups been larger.

The retrospective non controlled study by Brown *et al.* concerned 45 TEN patients with a mean TBSA epidermal detachment of 45%, 21 of which recieved standard care including surgical debridement in a burn unit, and the remaining 24 recieved similar standard care along with IVIG at a significantly lower than usual total dose of 1.6 g/kg.[47] In this study, mortality was 42% in the IVIG group versus 29% in the standard care group.Mortality in the IVIG treated group was also higher than that predicted by SCORTEN (38%). These results are somewhat surprising, and several features of this study are quite unusual.First, the standard care protocol is different from that used in most centers with experience in the management of TEN, in that wound debridement, a practice that is no longer recommended, is performed on all patients at admission. Second, the mortality rate of 42% observed in the IVIG treated group of patients is higher than that reported in epidemiological studies of TEN, and that historically observed with standard care in most experienced centers. This suggests that some individual or combined aspect of the management protocol for patients in the IVIG group of this study may differ from that of the other studies assessing the effect of IVIG in TEN. The association of IVIG treatment and debridement is certainly one difference between this and other studies.Third, the total dose of IVIG used is the lowest of all studies described herein as only 1.6 g/kg total dose of IVIG was administered, and lastly, the onset of IVIG treatment was quite late (average of 7 days after onset of disease).

Al-Mutairi *et al.* report 12 consecutive patients with TEN treated in Kuwait with a dose of 0.5–1.0 g/kg/d of IVIG for 4–5 days along with standard care protocol.[48] The average age of their patients was 27.16 years (7–50 years), including 4 children, and the average total body surface area involvement was 57.5%. All patients studied responded well to IVIG treatment. There was no mortality, and the progression of disease was arrested in a mean of 2.83 days (1–5 days).

Tan *et al.* have reported retrospective data from 8 patients with TEN and 4 patients with Stevens-Johnson syndrome-toxic epidermal necrolysis (SJS-TEN) overlap treated with high-dose IVIG in Singapore.[49] The total dose of IVIG administered was 2 g/kg body weight, with the exception of 2 patients who received a total dose of 1.5 g/kg body weight. The mean age of patients was 49.9+/−18.8 years (range, 19 to 70 years), but the mean surface of epidermal detachment is unfortunately not reported. Eleven of 12 patients (92%) survived, and in these patients the mean time to objective response was 3.6+/−1.9 days, suggesting that high-dose IVIG may be a safe and effective therapy for Asian patients with TEN.

Taken together, although all studies published to date are non-controlled, 7 of the 9 studies summarized in Figure 4 point towards a benefit of high dose IVIG upon the mortality associated with TEN. It should be noted that in the two studies that showed no benefit on mortality, the total dose of IVIG used was of 2 g/kg or less, whereas in 5 of the 7 studies showing a benefit of IVIG on mortality, the total dose of IVIG used was greater than 2 g/kg.

Use of IVIG for the treatment of SJS has also been reported, but conclusions are more difficult to draw as the mortality associated with this condition is usually low (1–5%). A total of three studies exist to date, two of which concern pediatric patients. In adults, Prins *et al*. have reported a series of 12 patients treated with a mean dose of 0.6 g/kg/d for an average of 4 days.[50] An objective response to IVIG infusion was observed within a mean of 2 days in 100% of treated patients with an overall survival rate of 100% and total skin healing in an average of 8.3 days. In pediatric patients, a first study by Morici *et al.* in which 7 children received IVIG (2 g/kg total dose) and 5 supportive care only, the authors report a significant reduction in the duration of fever for the IVIG-treated (8 days) versus supportive care (14 days) group. A second study by Metry *et al.*, retrospectively analyzed 7 children treated with IVIG (2g/kg total dose) and reported the absence of new blisters within 24–48 h of the initiation of IVIG, good outcome in all patients and the absence of side effects. High-dose IVIG seems therefore effective in blocking the progression of SJS and reducing the time to complete skin healing.

In conclusion, studies of the pathogenesis of TEN suggest that destruction of the epidermis, in the context of the ongoing drug-related hypersensitivity reaction, is due to massive Fas-mediated keratinocyte cell death by apoptosis. IVIG inhibits Fas-FasL interaction and cell death *in vitro*, and thus provides a rationale for use in humans. Since that discovery, 9 large non-controlled clinical studies have been published, and lower than expected mortality has been reported in 7 of these. Although each study has its potential biases, and the 9 studies are not strictly comparable, it appears from comparative analysis that IVIG at total doses of more than 2 g/kg are a safe and potentially useful treatment for TEN. Hopefully the cumulative results obtained in a non controlled manner to date

will serve as the basis for designing a prospective controlled trial in the near future. Such an approach appears the only way to definitively define the therapeutic potential of IVIG in TEN.

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