STUDY

Treatment of Toxic Epidermal Necrolysis With High-Dose Intravenous Immunoglobulins

Multicenter Retrospective Analysis of 48 Consecutive Cases

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Objective: To evaluate the effect of high-dose intravenous immunoglobulin (IVIG) in toxic epidermal necrolysis (TEN), parameters that may affect response to treatment, and the effect of different IVIG batches on Fas-mediated cell death.

Design: Multicenter retrospective analysis of 48 consecutive TEN patients treated with IVIG.

Setting: Fourteen university hospital dermatology centers in Europe and the United States.

Patients: Forty-eight patients with TEN (skin detachment >10% of their body surface [mean, 44.8%; range, 10%-95%]).

Interventions: Infusion of IVIG in all patients (range, 0.8-5.8 g/kg), and analysis of the ability of different IVIG batches to inhibit Fas-mediated cell death.

Main Outcome Measures: Objective response to IVIG treatment, final outcome at day 45, parameters that may affect response to IVIG treatment, and tolerance.

Results: Infusion of IVIG (mean total dose, 2.7 g/kg [range, 0.65-5.8 g/kg]; mean consecutive days, 4 [range, 1-5 days]) was associated with a rapid cessation (mean, 2.3 days [range, 1-6 days]) of skin and mucosal detachment in 43 patients (90%) and survival in 42 (88%). Patients who responded to IVIG had received treatment earlier in the course of disease and, on average, higher doses of IVIG. Furthermore, analysis of 35 IVIG batches revealed significant batch-to-batch variations in the capacity of IVIG to inhibit Fas-mediated cell death in vitro.

Conclusions: Early infusion of high-dose IVIG is safe, well tolerated, and likely to be effective in improving the survival of patients with TEN. We recommend early treatment with IVIG at a total dose of 3 g/kg over 3 consecutive days (1 g/kg per day for 3 days).

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TOXIC EPIDERMAL necrolysis (TEN, also known as Lyell syndrome) is an acute and life-threatening mucocutaneous disease that is almost always drug related. The disease occurs at an estimated incidence of 0.4 to 1.2 cases per million, and most frequently as a result of sulfonamide, anticonvulsivant, or nonsteroidal anti-inflammatory drug use.[1,2] It is a consequence of extensive keratinocyte apoptosis that results in the separation of large areas of skin at the dermoepidermal junction, producing the appearance of scalded skin. This extensive cell death also results in mucous membrane detachment and contributes to the characteristic symptoms of TEN that include high fever, extreme skin pain, anxiety, and asthenia.[1,2] Clinically, cases of TEN with the most extensive skin detachment are associated with the highest mortality, and when large case series are compiled, they point to an average mortality rate ranging between 25% and 35%.[3-5] However, studies analyzing elderly patients[6] indicate a rate of mortality averaging 50%.

The low prevalence of TEN makes randomized clinical trials difficult to perform. As a consequence, the relevant literature consists mostly of case reports and small uncontrolled series. These studies reveal that several treatments, including cyclosporine, cyclophosphamide, plasmapheresis, and *N*-acetylcysteine, have shown promising results[7-12]; they reveal, too, that the use of corticosteroids remains controversial and that it may even increase mortality.[13-16] Recently, a controlled study using thalidomide was interrupted because of a higher mortality rate in the thalido-

See also pages 33, 39, and 85

mide group (10 of 12 patients died) than in the placebo group (3 of 10 died).[17]

Because the extent of epidermal detachment is an important prognostic factor in TEN,[1,18] therapeutic modalities that inhibit apoptosis are likely to be the most useful in the early phase of the disease. Apoptosis is a tightly controlled form of cell death that can be triggered by various stimuli, including signaling by cell-surface death receptors such as Fas. We recently elucidated the mechanisms involved in triggering keratinocyte apoptosis during TEN. We demonstrated that keratinocyte apoptosis occurs as a result of enhanced keratinocyte FasL (CD95L) expression, which induces Fas-mediated keratinocyte cell death.[19] We also showed that commercially available intravenous immunoglobulin (IVIG) preparations inhibited the progression of TEN in 10 patients treated in a pilot study.[19] A few other case reports have documented the treatment of TEN with IVIG.[20-22] In addition, we demonstrated that IVIG contains anti-Fas antibodies able to inhibit Fas-mediated keratinocyte apoptosis in vitro.

In this study we expand our preliminary observations and report the retrospective analysis of 48 TEN patients treated with standard care and IVIG at a mean total dose of 2.7 g/kg (range, 0.8-5.8 g/kg) over a mean of 4 consecutive days (range, 1-5 days). Objective response to IVIG treatment, final outcome at day 45, as well as parameters that may affect response to IVIG treatment and tolerance were assessed.

Finally, because the therapeutic effect of IVIG in TEN is thought to arise from the inhibition of Fas-mediated cell death by antagonistic anti-Fas antibodies, and little is known about the constance of this inhibitory effect in different commercialized batches of IVIG, we analyzed the Fas-inhibitory activity of a large series of commercialized IVIG batches and a few samples of IVIG perfusions used in study patients.

METHODS

PATIENTS

The 48 consecutive patients retrospectively studied were diagnosed as having TEN according to established clinical and histological criteria.[1] Diagnosis of TEN was confirmed in all but 5 cases by histological examination of lesional skin showing full-thickness epidermal necrolysis. This procedure excluded staphylococcal scalded skin syndrome and other, less likely differential diagnoses. The patients were hospitalized in 14 university-based dermatology centers within Europe (Switzerland [17], Germany [4], Italy [8], France [5]) and the United States (14) between July 1997 and July 2000. Patient demographics are shown in **Table 1**.

Patients were considered eligible to participate in this retrospective study if the confluence of cutaneous lesions led to large areas of detached and/or detachable epidermis covering at least 10% of their total body surface area (TBSA). According to a consensus definition for the classification of Stevens-Johnson syndrome (≤10% of TBSA detachment) and TEN,[23] our criteria allowed selection of cases of Stevens-Johnson syndrome–TEN overlap (10%-30% of TBSA epidermal detachment) as well as TEN (>30% of TBSA epidermal detachment). Cases of Stevens-Johnson syndrome, which are known to have a lower mortality rate, were thus eliminated. In all cases clinical examination was performed by senior dermatologists with experience in the evaluation of TEN. Photographic documentation of at least 1 case per center was reviewed to ascertain consensus regarding the evaluation of epidermal detachment (**Figure 1**). In each case a consensus on the percentage of TBSA epidermal detachment occurred between the senior dermatologist in charge of the patient at one of the 14 centers and the study coordinators (C.P. and L.E.F.) who evaluated photographic documents. All patients had progressive epidermal detachment at treatment initiation, and none was excluded from the study because of epidermal detachment greater than 90% of TBSA. All cases of each study center were analyzed to minimize potential selection bias. The putative culprit drug(s) was identified in 45 (94%) of 48 patients (**Table 2**).

Table 1. Patient Demographics

No. of patients	48
Age, y	
Mean ± SD	43 ± 24
Range	4-95
Male/female, No.	24/24
Skin detachment, % of total body surface area	
Mean ± SD	44.8 ± 22.5
Range	10-95
Mucous membrane involvement, % of cases	91.7

TREATMENT WITH HIGH-DOSE IVIG

Patients were treated with standard care and commercially available IVIG (Sandoglobulin [Novartis, Basel, Switzerland], Endobulin [Baxter, Deerfield, Ill], Gammagard [Baxter], Gamimmune-N [Bayer, Leverkusen, Germany], Polygam [American Red Cross, Washington, DC], Gammar-P IV [Centeon-Aventis Behring, King of Prussia, Pa], Intraglobin-F [Biotest Pharma, Dreieich, Germany], or Octagam [Octapharma, Lachen, Switzerland]) at doses of 0.2 to 2.9 g/kg per day (mean, 0.7 g/kg per day) for 1 to 5 consecutive days (mean, 4 days). No specific protocol was used by all participating centers, and the decisions of when to initiate IVIG treatment and what dose to administer were determined by each center. Patients were treated in standard hospital floors rather than burn units, or in intensive care units if advanced life support was required. They did not receive any of the other therapies that have been suggested to be effective in TEN (cyclosporine, plasmapheresis, cyclophosphamide, and *N*-acetylcysteine). Twelve patients (25%) had received oral or intravenous corticosteroids prior to initiation of IVIG infusion without improvement in TEN symptoms.

CLINICAL ANALYSES AND OUTCOME MEASURES

For each patient treated with IVIG, the following clinical parameters were recorded and analyzed: age; sex; histological diagnosis; presence or absence of mucosal involvement; TBSA percentage of detached skin (erosion, blisters, and areas with positive Nikolsky sign) according to an illustrated atlas and using the rule of nines as in burn patients[23,24]; putative causal drug(s); other drugs taken at the onset of TEN; IVIG dosage (grams per kilograms of body weight per day); IVIG manufacturer; time in days from first sign of epidermal or mucosal detachment to initiation of IVIG infusion; presence or absence of an objective response to treatment defined by an interruption of further epidermal or mucosal detachment; time in days to response (interruption of further epidermal or mucosal detachment); final outcome at 45 days (deceased or alive); pres-

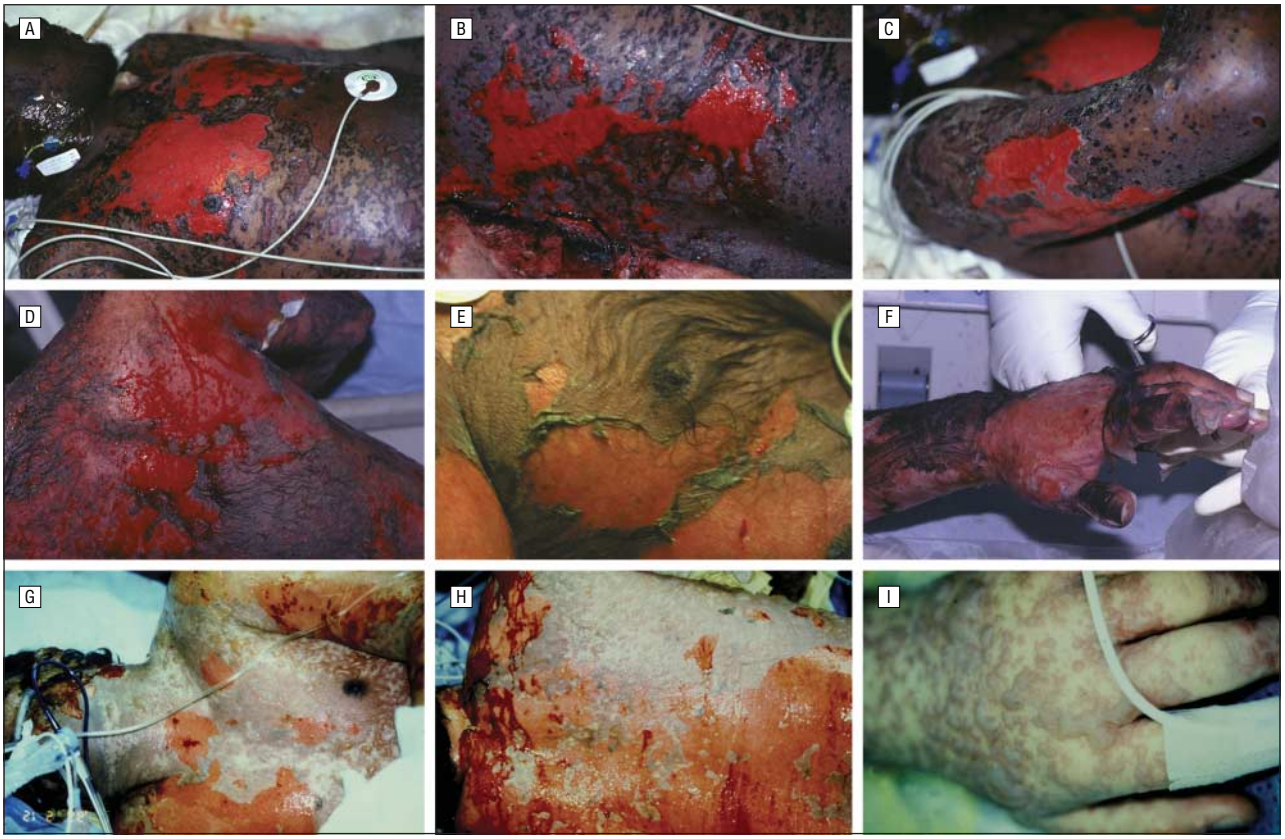

Figure 1. Epidermal detachment in patients 31 (A-C), 32 (D-F), and 37 (G-I) was 30%, 70%, and 70% of total body surface, respectively, at the time of initiation of intravenous immunoglobulin infusion.

ence or absence of sequelae (ocular, Sjögren-like sicca syndrome, other); tolerance to IVIG (no adverse effects); presence or absence of a concurrent underlying disease (if so, type of disease); and time at which the putative causal drug(s) was stopped.

The main end point of the study was mortality at day 45. Time to objective clinical response was also evaluated.

STATISTICAL ANALYSIS

All clinical parameters are expressed as mean ± SD. To assess the magnitude of the effect of a given clinical parameter, single independent variable and multiple independent variable logistic regression models were used to estimate odds ratios (ORs). Both unadjusted and adjusted ORs are estimated with 95% confidence intervals (CIs). However, because no differences were appreciated between the 2 models, only the single independent variable models are reported. Two-way interaction terms were considered between the patient's site of hospitalization and the clinical parameters. These interactions were not significant ($P>.10$) and are therefore not reported. Finally, random-effect models clustering on country of origin were also considered. Parameter estimates and 95% CIs were not appreciably changed, and we only report our primary analysis, which was a fixed-effect model. Reported P values are for the Wald statistic. Statistical analyses were conducted using Stata for Windows 95/NT version 6.0 (Stata Corp, College Station, Tex).

MEASUREMENT OF THE FAS-INHIBITORY ACTIVITY OF IVIG BATCHES

Fas-inhibitory activity was measured in commercially available IVIG from 2 producers (Sandoglobulin [Novartis/ZLB] and Gammagard S/D, Endobulin, or Endobulin S/D [Baxter]), and in samples of IVIG used to treat certain study patients. Briefly, A20 lymphoblastoid cells were preincubated for 2 hours with a range of IVIG concentrations and then incubated for 16 hours in the presence of 50 ng/mL of recombinant sFasL (Alexis Corp, San Diego, Calif) plus 1 µg/mL of enhancer (Alexis Corp). Cellular viability was determined using the WST cell proliferation assay (Roche Diagnostics, Rotkreutz, Switzerland). The dose of IVIG, in milligrams per milliliter, leading to 50% inhibition of cell death was calculated, and Fas-inhibitory activity was measured using a standardized FasL-mediated cell death assay and reported as $1/IC_{50}$ (IC_{50} being the concentration of IVIG required to achieve 50% inhibition of FasL-mediated cell death).

To quantify anti-Fas antibody content within IVIG, 1 µg of purified fusion recombinant protein (Fas-comp) or control recombinant protein (comp)[25] were first subjected to 8% sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) under reducing conditions; then immunoblotted with either IVIG (60 µg/mL) or monoclonal mouse antihuman Fas antibody (Apo-1; Pharmingen, San Diego, Calif), followed by 1:2000 antihuman IgG-HRP (Dako Corp, Glostrup, Denmark) or 1:2000 antimouse IgG-HRP Fab specific (Sigma, St Louis, Mo), respectively; and finally revealed using the ECL system (Amersham, Piscataway, NJ).

RESULTS

PATIENT CHARACTERISTICS

Forty-eight patients with TEN were treated with standard care and high-dose IVIG in 14 university dermatology centers in Europe and the United States between

Table 2. Outcome of 48 Cases of TEN Treated With High-Dose IVIG

Patient No./ Sex/Age, y	Skin Detachment (% of TBSA)	Putative Drug(s)	Total Dose of IVIG, g/kg	Time to Treatment Initiation, d	Time to Objective Response, d	Outcome
1/M/23	50	Ibuprofen	3	5	2	Survived
2/F/22	30	Carbamazepine sodium	3	4	1	Survived
3/F/57	30	Ciprofloxacin hydrochloride	1.5	3	2	Survived
4/F/89	60	Co-trimoxazole	3	4	2	Survived
5/F/24	30	Paracetamol (acetaminophen)	3	3	2	Survived
6/M/61	20	Phenytoin sodium	2.25	5	2	Survived
7/F/25	40	Phenobarbital sodium	3	4	3	Survived
8/M/11	20	Acetylsal ac	3	4	2	Survived
9/M/29	60	Amox-clav	2.25	2	4	Survived
10/M/26	60	Ceftriaxone sodium	3	2	1	Survived
11/M/77	45	Amox-clav	2.25	4	3	Survived
12/M/13	40	Cefuroxime axetil	1.8	2	2	Survived
13/M/65	30	Doxycycline monohydrate	3	4	2	Survived
14/F/7	10	Carbamazepine sodium	2.25	3	2	Survived
15/M/75	30	Pentamidine	3	10	. . .	Death
16/M/28	30	Phenytoin sodium	3.75	9	1	Survived
17/F/60	40	Omeprazole sodium	2.4	7	5	Survived
18/F/44	18	Uromitoxan	0.8	4	1	Survived
19/F/4	26	Paracetamol	2	8	2	Survived
20/F/20	70	Acetylsal ac	2	7	2	Survived
21/F/21	40	Pyrantel pamoate	2	10	2	Survived
22/F/95	30	Ketoprofen	2	10	2	Survived
23/F/35	35	ND	2	12	2	Survived
24/F/44	70	Nimesulide	2	15	2	Survived
25/M/75	95	Phenobarbital sodium	2	10	. . .	Death
26/M/29	50	Paracetamol	2.2	2	2	Survived
27/F/64	20	Allopurinol	3.5	3	1	Survived
28/F/39	50	Ampicillin	2.5	5	2	Survived
29/M/43	30	Co-trimoxazole	4	7	2	Survived
30/M/62	40	Carbamazepine sodium	4	30	5	Survived
31/M/34	30	Nevirapine	4	30	2	Survived
32/M/45	70	Allopurinol	4	14	6	Survived
33/F/48	30	Furosemide	1.6	14	4	Death
34/F/54	60	Carbamazepine sodium	4	7	3	Survived
35/F/52	90	Acetazolamide sodium	1.6	15	. . .	Death
36/M/70	90	Carbamazepine sodium	2.4	9	. . .	Death
37/M/16	70	Co-trimoxazole	2.4	5	1	Survived
38/M/4	95	Phenobarbital sodium	2.4	7	ND	Survived
39/F/45	60	Ceftriaxone sodium	2.4	8	1	Survived
40/F/64	50	Amox-clav	0.65	3	2	Survived
41/F/77	55	Carbamazepine sodium	1.5	3	. . .	Death
42/M/16	20	ND	3	3	3	Survived
43/M/7	30	Phenobarbital sodium	5.8	8	1	Survived
44/M/45	40	Sulfasalazine	2.5	2	2	Survived
45/F/47	27	Allopurinol	4	3	3	Survived
46/M/60	25	Carbamazepine sodium	4	7	1	Survived
47/M/38	90	Vancomycin hydrochloride	4	5	2	Survived
48/F/74	20	ND	1.7	7	2	Survived

Abbreviations: Acetylsal ac, acetylsalicylic acid; Amox-clav, amoxicillin trihydrate and clavulanic acid; IVIG, intravenous immunoglobulin; ND, not determined; TEN, toxic epidermal necrolysis.

July 1997 and July 2000. Data from these patients, shown in Table 1, were retrospectively analyzed. All patients had mucosal involvement and detachment of the epidermis affecting 10% or more of their TBSA (Table 1 and Figure 1).

HIGH-DOSE IVIG TREATMENT AND RESPONSE

In addition to standard care, all patients received infusions of IVIG immediately upon diagnosis and/or admission to a study center. Infusions of IVIG were initiated on average 7 days (range, 2-30 days) after the onset of TEN and given over a period of 1 to 5 days (mean, 4 days) at a mean total dose of 2.7 g/kg (range, 0.65-5.8 g/kg) (Table 2 and **Table 3**). An objective response to IVIG, defined as the interruption of the progression of epidermal necrolysis, was observed in 43 (90%) of the 48 patients (Table 3).

All but 1 of the 43 patients who initially responded to IVIG achieved complete healing of skin and mucous membrane lesions within an average of 15 days (range, 4-40 days). All of these 42 patients also survived TEN, for a survival rate at 45 days of 88% (Tables 2 and 3, and

Table 3. Characteristics of the IVIG Treatment and Clinical Response*

Time from onset of TEN to IVIG treatment, d	7.3 ± 6 (2-30)
Total dose of IVIG, g/kg	2.7 ± 1 (0.65-5.8)
Daily dose of IVIG, g/kg	0.7 ± 0.4 (0.375-2.9)
Time to objective response, d	2.3 ± 1.2 (1-6)
Duration of IVIG treatment, d	4 ± 0.9 (1-5)
Objective response rate, %	90 (43/48 patients)
Survival rate, %	88 (42/48 patients)
Time to complete skin healing, d	15 ± 9.5 (4-40)

Abbreviations: IVIG, intravenous immunoglobulin; TEN, toxic epidermal necrolysis.
*Data are given as mean ± SD (range) unless otherwise specified.

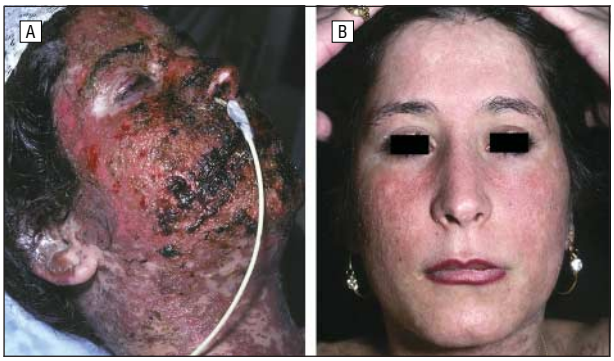

Figure 2. Representative images of the skin of patient 2 before (A) and 30 days after (B) initiation of intravenous immunoglobulin therapy.

Figure 2). The patient who died despite responding to IVIG died from myocardial infarction, a cause deemed unrelated to TEN. Mucosal lesions responded in a manner similar to skin lesions and no ocular or mucous sequelae were reported. Tolerance to IVIG treatment was good in all cases, as no severe adverse effects were reported as a consequence of IVIG infusion. However, a dose reduction of IVIG is recommended in patients with renal insufficiency to limit the risk of transient acute renal insufficiency due to proximal tubular dysfunction.

PARAMETERS ASSOCIATED WITH NONRESPONSE TO HIGH-DOSE IVIG

Therapeutic and clinical parameters that may affect patients' responsiveness to IVIG treatment and/or likelihood of survival were analyzed. As expected, and in agreement with published data from large case studies,[3-5] increased age and greater surface of epidermal detachment were both associated with a worse prognosis. In our study, the mean age was 39.6 years (range, 4-95 years) and surface of epidermal detachment was 42% (range, 10%-95%) in the group of patients who ultimately survived, compared with 66.2 years (48-77 years) and 65% (range, 30%-95%), respectively, in the group of patients who died (**Table 4**). The odds of survival decreased per year of life (OR, 1.06; 95% CI, 1.01-1.11; $P=.02$) and with increasing epidermal detachment (OR, 1.04; 95%CI, 1.01-1.08; $P=.03$).

Comparison of the groups of surviving and deceased patients further revealed that IVIG infusions were initiated, on average, on day 7 (range, 2-30 days) in those who responded to treatment and on day 10 (range, 3-15 days) in those who died ($P=.22$) (Table 4). In the latter group the average total dose of IVIG infused was 2 g/kg (range, 1.5-3 g/kg), and in patients who survived it was 2.8 g/kg (range, 0.65-5.8 g/kg) ($P=.08$). Also, underlying disease was observed in 100% of patients with TEN who died despite IVIG infusion, compared with 52.3% in the group of survivors ($P=.03$) (Table 4). Each of these diseases—renal and/or cardiovascular insufficiency (50% vs 5%), ischemic and/or hypertensive disease (67% vs 12%), infectious disease (33% vs 12%), and cancer (33% vs 10%)—was more frequently observed in the group of patients who died (Table 4). Two of the 48 patients had tested positive for human immunodeficiency virus (patients 29 and 31), and both survived (Table 2).

Prior use of systemic corticosteroids was slightly but not significantly more frequent (26% vs 17%) in the group of patients who survived (Table 4).

VARIABILITY IN FAS-INHIBITORY ACTIVITY OF IVIG

Based on our recent discovery that Fas is implicated in the pathogenesis of TEN and that IVIG can specifically inhibit Fas-mediated cell death, we suggest that one possible cause of variability in the response of patients with TEN to IVIG treatment is a variability in the Fas-inhibitory activity of the IVIG batches used.

The Fas-inhibitory activity of IVIG can be measured using a standardized in vitro cell death assay that quantifies the ability of IVIG to inhibit cell death caused by a fixed concentration of recombinant Fas ligand. This analysis was performed on a large array of batches of 3 commercialized forms of IVIG. The Fas-inhibitory activity ($1/IC_{50}$) of IVIG batches is very variable, ranging from 0 to a maximum of 2 (average, 0.75). Immunoblotting showed the observed batch-to-batch variation in Fas-inhibitory activity to be due to differences in anti-Fas antibody content within IVIG batches. The number of Gammagard S/D and Endobulin batches analyzed was too small to compare their mean inhibitory activity with that of Sandoglobulin.

Finally, analysis of IVIG samples collected from the IVIG perfusions used to treat patients was retrospectively performed for 7 of the 48 patients. Of these 7 patients, 6 (patients 3-7 and 10) had responded to IVIG and 1 (patient 15) had not. Variability in the Fas-inhibitory activity of the different IVIG samples was again observed; however, no reduction of Fas-inhibitory activity was detected in the IVIG used to treat the single patient who did not clinically respond to IVIG treatment of TEN.

COMMENT

TEN is characterized by the rapid onset of extensive keratinocyte apoptosis and epidermal detachment accompanied by a high rate of mortality.[1] We have shown that the pathogenesis of TEN involves Fas-mediated apoptosis of keratinocytes, and that it occurs when keratinocytes strongly induce expression of the cytolytic molecule FasL.[19] Furthermore, we previously demonstrated

Table 4. Comparison of Therapeutic and Clinical Parameters in Treated Patients Who Survived and Died*

Parameter	Survived (n = 42)	Died (n = 6)
Age, y	39.6 ± 23.2 (4-95)	66.2 ± 12.8 (48-77)
Skin detachment, % of TBSA	42 ± 20 (10-95)	65 ± 30.7 (30-95)
Time to IVIG treatment, d	6.8 ± 6.1 (2-30)	10.2 ± 4.3 (3-15)
Total dose of IVIG, g/kg	2.8 ± 1 (0.65-5.8)	2.0 ± 0.59 (1.5-3)
Underlying disease, No. (%) of cases	22 (52)	6 (100)
Renal and/or cardiovascular insufficiency	2 (5)	3 (50)
Ischemic and/or hypertensive disease	5 (12)	4 (67)
Cancer	4 (10)	2 (33)
Infectious disease	5 (12)	2 (33)
Prior use of systemic corticosteroids for TEN, % of cases	11 (26)	1 (17)

Abbreviations: IVIG, intravenous immunoglobin; TBSA, total body surface area; TEN, toxic epidermal necrolysis.
*Data are given as mean ± SD (range) unless otherwise specified.

that Fas-mediated keratinocyte cell death can be potently inhibited by IVIG in vitro, and this provided the rationale for investigating the therapeutic potential of IVIG in the treatment of TEN.

This retrospective multicenter study, which was conducted to gather sufficient preliminary information for preparing a randomized controlled trial, is the largest therapeutic study of TEN reported to date. It assessed, in a preliminary, retrospective, noncontrolled, and multicenter manner, the effect of IVIG together with standard supportive care in 48 patients with severe TEN. The results show that with this treatment rapid and complete inhibition of ongoing epidermal necrolysis occurred in 43 (90%) of 48 patients, resulting in a survival rate of 88% (42 patients) at day 45.

The rate of survival observed in our study is very encouraging when compared with that reported in large case studies in which supportive therapy was used alone as the accepted standard of care.[3-5] However, as the most recent of these studies were performed over 10 years ago, and none of them were controlled, definitive conclusions concerning the efficacy of IVIG compared with standard care cannot be made. With these concerns in mind, it is interesting that in patient groups with similar characteristics—eg, average age (45.8 years in the Revuz et al[3] study, 46.8 years in the Roujeau et al[4] study, and 43 years in this study) and percentage of TBSA epidermal detachment (38.9% in the Revuz study, 47.5% in the Roujeau study, and 44.8% in this study)—the survival rate of 88% that we report using IVIG together with supportive therapy is higher than the rates reported by Revuz et al or Roujeau et al for supportive therapy alone (75% and 70%, respectively). These promising results warrant a randomized controlled study of the efficacy of IVIG in addition to supportive care in the treatment of TEN.

At least 2 biases may have affected our results. The first is an information bias because we did not systematically reevaluate the extent of body surface detachment for all patients. However, at least 1 case from each center was reviewed from photographs to ensure consensus on the evaluation of epidermal detachment and limit the possibility of overevaluation. Second, although contributing centers were asked to report all cases of TEN treated with IVIG, we cannot completely exclude the possibility of a reporting bias. Despite these possible limitations, we think that our results are reliable because they reproduce results previously reported concerning the correlation of age and extent of epidermal detachment with final outcome[3,4]; moreover, the 48 cases studied were contributed by 14 centers, and this limited any possible center effect. Finally, we chose not to exclude patients with epidermal detachment greater than 90% of their TBSA (2 patients, 1 of whom died) although these patients had a bad prognosis.

Analysis of clinical and therapeutic parameters of the group of patients who survived after IVIG infusion and the group of patients who died (Table 4) revealed interesting differences that may help define the optimal conditions for this therapeutic approach. First, IVIG infusion was shown to be initiated later in patients who died. Second, the total dose of IVIG received by patients who died was lower than that received by patients who survived. Third, the coexistence of an underlying chronic disease—eg, renal and/or cardiovascular insufficiency, ischemic and/or hypertensive disease, cancer, or infectious disease—was more frequent in the group of patients who died. Although these data are preliminary, they suggest that factors such as time to initiation of IVIG infusion, total dose of IVIG infused, and presence of severe underlying disease may affect the outcome of TEN patients treated with IVIG.

This study also demonstrates for the first time that the potential of IVIG to inhibit Fas-mediated cell death is very variable from batch to batch, and that although batches devoid of Fas-inhibitory activity were not among those used to treat patients in our study, they do occur. For logistic reasons we were only able to measure the Fas-inhibitory activity of IVIG used to treat 1 of the 6 patients not responding to IVIG in addition to supportive therapy. In this case, anti-Fas activity was conserved. Whether variability in the Fas-inhibitory activity of IVIG can have an effect on the clinical response to IVIG therapy in TEN remains to be determined. To clarify this issue, the anti-Fas activity of IVIG batches used to treat nonresponding patients should be studied systematically in a larger series.

Finally, although the data reported here and previously[19] favor the concept that the observed effect of IVIG in TEN is due to in vivo inhibition of Fas-mediated ke-

ratinocyte death, other effects of IVIG cannot be excluded. Patients with TEN are prone to infectious complications[1,2,26] that IVIG infusion may limit through its anti-infectious properties.[27] Furthermore, as in burn patients, large fluid and protein losses occur in TEN patients. Infusion of IVIG, which not only restores protein but also fluid, may help limit the extent of fluid loss that occurs through the denuded skin.

From this retrospective study we provide evidence suggesting that IVIG infusion, in combination with standard supportive therapy, is a useful and safe therapeutic approach for TEN. From our experience of 48 cases of TEN, we recommend early treatment in a hospital setting with IVIG at a total dose of 3 g/kg over 3 consecutive days (1 g/kg per day for 3 days). The new data here presented pave the way for a controlled trial of the clinical efficacy of IVIG in TEN.

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