

Intravenous immunoglobulins in the treatment of severe drug eruptions

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Purpose of review

To present and discuss the rationale for using high-dose intravenous human immunoglobulins in the treatment of severe drug eruptions and the clinical results of recently published series.

Recent findings

In toxic epidermal necrolysis, intravenous human immunoglobulins were expected to inhibit the apoptosis of epidermal cells by blocking the *Fas*/*Fas* ligand pathway. Some controversies persist both on the role of *Fas*/*Fas* ligand pathway and on the anti-apoptotic effect of human immunoglobulins *in vitro*. The clinical results of the treatment of toxic epidermal necrolysis with intravenous immunoglobulins are also controversial, the important differences between series being difficult to explain.

Summary

More evidence is needed before high-dose intravenous human immunoglobulins can be considered as standard therapy of toxic epidermal necrolysis.

Keywords

toxic epidermal necrolysis, apoptosis, intravenous immunoglobulins

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Abbreviations

IVIG intravenous immunoglobulin
SJS Stevens–Johnson syndrome
TEN toxic epidermal necrolysis

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Introduction

Severe drug eruptions are those that are life-threatening, need hospitalization or result in some disability. The main drug eruptions fitting this definition are Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms. The main characteristics of these reactions are presented in Table 1 [1].

Acute generalized exanthematous pustulosis is a less severe cutaneous drug eruption with a low risk of mortality. To our knowledge no treatment with human intravenous immunoglobulins (IVIGs) has been reported for this indication.

Few cases of drug reaction with eosinophilia and systemic symptoms treated by IVIG have been published [2]. We will focus on in-vitro and in-vivo arguments for the use of IVIGs in SJS and TEN.

Rationale for using intravenous immunoglobulins in toxic epidermal necrolysis

SJS and TEN are severe drug reactions characterized by the destruction of epithelial cells from the skin (epidermis) and mucous membrane, resulting in widespread blisters, the detachment of necrotic epidermis and erosions. The extent of erosions is limited to less than 10% of the total skin surface in SJS and is more widespread in SJS/TEN overlapping cases and in TEN. The mortality rate is 5–10% for SJS and 30–40% for TEN.

The destruction of epithelia is the result of massive apoptosis [3]. It has been suggested that in TEN this apoptosis of epithelial cells was principally mediated through the activation of the *Fas* (CD95) receptor, and that commercial preparations of human immunoglobulins contained variable amounts of *Fas*-blocking antibodies capable of inhibiting the activation of the death receptor [4]. These in-vitro results, associated with the report of a favourable outcome in a short series of patients treated with IVIGs, created an immediate enthusiasm for this new treatment for SJS, TEN and other severe drug reactions.

Table 1. Usual clinical and biological findings of severe drug eruptions

	SJS	TEN	Hypersensitivity/DRESS
Mucous membrane	> 90%	> 90%	< 30%
Erosions	Several sites	Several sites	Mouth and lips
Detachment of epidermis	Yes < 10% of BSA	Yes $\geq$ 30% of BSA ^a	No
Hyperkeratosis/desquamation	No	No	Usual
Neutropenia	No	30%	No
Eosinophilia	No	No	90%
Atypical lymphocytes	No	No	30–40%
Respiratory tract	Bronchial erosions/ARDS	Bronchial erosions/ARDS	Interstitial pneumonitis
Liver	Hepatitis 10%	Hepatitis 10%	Hepatitis 60%
Heart	No	No	Myocarditis
Lymph node enlarged	No	No	Usual

ARDS, Adult respiratory distress syndrome; BSA, body surface area; DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis. ^aWhen detachment involves 10–29% of BSA, we classify the case as SJS–TEN overlap. Reproduced from Bachot and Roujeau [1].

A key role of *Fas*/*Fas* ligand in Stevens–Johnson syndrome/toxic epidermal necrolysis?

In 1998, Viard *et al.* [5] suggested that the *Fas*/*Fas* ligand pathway played a key role in the apoptosis of epidermal cells in TEN. They showed an upregulation of *Fas* ligand on the cell membrane of keratinocytes in the lesional skin of patients with TEN. The *Fas* ligand protein interacts with the death receptor *Fas* (or CD95). On contact with the *Fas* ligand, cells expressing *Fas* rapidly undergo apoptosis [4]. *Fas* ligand expressed on keratinocytes was functionally active. Fragments of ‘necrotic’ epidermis from TEN patients were cytotoxic for *Fas*-sensitive cell lines (Jurkat). This cytolytic activity of epidermal cells on Jurkat cells could be blocked by monoclonal antibodies that interfered with the interaction of *Fas* and *Fas* ligand. It was also abolished by a high concentration of normal human immunoglobulins. IVIGs inhibited *Fas*-mediated cell death by blocking the *Fas* receptor rather than by interacting with the *Fas* ligand.

It was inferred that keratinocytes overexpressing *Fas* ligand could kill neighbouring keratinocytes that constitutively express *Fas*, but this was not directly shown in the paper. As human keratinocytes were approximately 10 times less susceptible than Jurkat cells to serum soluble *Fas* ligand-induced apoptosis, it is a pity that this key experiment had not been performed. Without this important step it is difficult to accept as evidence that *Fas*/*Fas* ligand interaction is the key determinant of apoptosis in TEN.

A more recent paper from the same group demonstrated that the *Fas* ligand was present mostly within the cytoplasm of normal keratinocytes, whereas *Fas* protein was expressed in keratinocytes of all subcorneal layers of the epidermis [6•].

Abe *et al.* [7•] found increased serum soluble *Fas* ligand concentrations in all samples of TEN and SJS patients,

whereas *Fas*, but not *Fas* ligand, expression was detected on keratinocytes from lesions of TEN patients as well as from normal skin. Soluble *Fas* ligand is cleaved from a membrane-bound *Fas* ligand by a matrix metalloproteinase-like enzyme, and also has the potential to mediate apoptosis. The sera of TEN and SJS patients mediated keratinocyte apoptosis *in vitro* [7•]. In addition, serum soluble *Fas* ligand secretion and *Fas* ligand messenger RNA levels were upregulated in blood lymphocytes of TEN patients by the causal drug. The authors concluded that serum soluble *Fas* ligand originating from blood lymphocytes, but not from keratinocytes, played a crucial role in the pathomechanism of TEN and SJS. It should be noted that keratinocyte apoptosis was induced by 100 ng/ml serum soluble *Fas* ligand when serum concentration of serum soluble *Fas* ligand was approximately 100 pg/ml, i.e. 1000 times lower.

Another study by Paquet *et al.* [8•] confirmed the findings of the above report that *Fas* was not overexpressed in lesional skin of TEN, but was usually only detected on the keratinocytes of the basal layer. It is therefore difficult to attribute to *Fas* activation the full thickness destruction of the epidermis.

Posadas *et al.* [9••] evaluated the synthesis of apoptosis-related cytokines by blood lymphocytes in a variety of drug reactions and local production in SJS or TEN blisters. They found larger increases in the local production of TNF- α , perforin, and granzyme B than in the synthesis of the *Fas* ligand [9••].

Nassif *et al.* [10••] looked at the role of lymphocytes present in the skin blisters of patients with TEN as probable effectors of this immune reaction. In a patient suffering from cotrimoxazole-induced TEN, blister fluid cells were phenotyped by fluorescence-activated cell sorter and tested for activity. Without any stimulation, the blister fluid lymphocytes exhibited a drug-specific

cytotoxicity on autologous cells. The lysis was blocked by an anti-MHC class I monoclonal antibody. It was abolished by ethylene glycol-bis-(2-aminoethyl ether) tetraacetic acid and by concanamycin A but neither by anti-*Fas*, nor by anti-TRAIL (tumor necrosis factor-related apoptosis inducing ligand) receptor monoclonal antibodies. These results strongly suggested perforin/granzyme-mediated cytotoxicity, without the implication of *Fas* at this stage.

Taken together, the above papers do not provide strong support to the hypothesis that epidermal cell apoptosis in SJS and TEN results mainly from a suicidal interaction between *Fas* and *Fas* ligand on keratinocytes.

Are intravenous immunoglobulins efficient and reproducible *Fas*-blocking agents?

This is also a controversial matter. In the landmark paper by Viard *et al.* [5], IVIG inhibited the lysis of Jurkat T cells by TEN epidermis. Any possible effect of IVIG on Jurkat cells in the absence of *Fas* ligand positive keratinocytes was not shown. This question is relevant because at the same time Prasad *et al.* [11] demonstrated that IVIG induced apoptosis of several cell lines of lymphocytes and monocytes by activating the *Fas* apoptotic pathway. In the same brand of IVIG as the one used by Viard *et al.* [5], they showed the presence of anti-*Fas* antibodies that can efficiently induce apoptosis.

In another study, Ekberg *et al.* [12] investigated whether IVIG could alter the pattern of apoptosis. After incubation with IVIG the incidence of apoptosis was elevated in activated CD95-positive peripheral blood mononuclear cells, whereas it was lower in small, non-activated cells.

Ghio *et al.* [13] also found elevated amounts of soluble *Fas* ligand molecules in some IVIG preparations.

A recent publication demonstrated that IVIG induced the apoptosis of human umbilical vein endothelial cells prestimulated by TNF- α *in vitro* [14••]. IVIG decreased the intracellular expression of anti-apoptotic proteins of the Bcl-2 family (A1 and Bcl-XL), whereas IVIG increased the intracellular expression of pro-apoptotic proteins (Bax and Bcl-XS). Furthermore, IVIG increased the intracellular production of reactive oxygen species and decreased the mitochondrial membrane potential. These results show a novel action in which IVIG can induce the apoptosis of TNF- α -stimulated cells through a mitochondrial apoptotic signalling pathway.

Taken together, such studies suggest that depending on experimental conditions IVIG can behave either as inducers or as inhibitors of apoptosis.

Other immunomodulatory effects of intravenous immunoglobulins

Obtained from pooled plasma from more than 1000 normal individuals, IVIGs contain antibodies against external antigens, autoantibodies and anti-idiotypes. The antibodies are exclusively IgG with a half-life and distribution equivalent to the IgG of normal serum. IVIG therapy has been reported to be effective in a large number of autoimmune diseases. However, the number of diseases with a well-documented therapeutic effect (randomized controlled trials) is limited [15]. The immunomodulatory effect of IVIG is dependent on [15]: interaction of the Fc portion of IVIG with Fc receptors on leukocyte surfaces; interaction of infused IgG with complement components; modulation of synthesis and release of cytokines produced by lymphocytes and monocytes; neutralization of circulating autoantibodies by infused IgG (anti-idiotypic); deviation of immune repertoire; interaction of IVIG with numerous other molecules on the surface of T and B cells.

Clinical studies with intravenous immunoglobulins in toxic epidermal necrolysis

A few publications had preceded and many followed the paper by Viard *et al.* [5]. Some were anecdotal reports with one or a few patients [16,17]. We will focus on seven main studies.

Two studies concerned paediatric cases

Morici *et al.* [18] retrospectively analysed the charts of 12 patients with SJS: seven were treated with IVIG, two with corticosteroids, and three with supportive care. IVIG was administered in a single infusion at 1.5–2 g/kg, on an average of 3 days after hospitalization. There was a trend towards a more rapid improvement of fever with IVIG. It is not clear whether some cases were not erythema multiforme major rather than SJS.

Tristani-Firouzi *et al.* [19] reported their experience in eight children treated for TEN with IVIG in a period of 3 years. The mean body surface involvement was 67%, the doses of IVIG were 0.5–0.75 g/kg per day for four consecutive days. The brand of IVIG was not specified. The average time to the arrest in the progression of lesions was 2.1 days and to the completion of re-epithelialization it was 8.1 days. All children survived. The authors compared them with a historical group of three patients with whom statistical comparison was not possible. It was established that the spontaneous prognosis of TEN in children is much better than in adults (5% of mortality) with faster re-epithelialization [20].

Five studies concerned mainly adults

The first series was included in an initial publication by Viard and the Geneva team [5]. In an open study, 10

consecutive patients with TEN or SJS (average skin detachment 28.5%; range 5 to 60%) were treated with IGIV (Sandoglobulin, Novartis, Bern, Switzerland) at doses ranging from 0.2 to 0.75 g/kg of body weight per day for four consecutive days. In all 10 patients the progression of skin disease was rapidly interrupted after IVIG infusion (within 24–48 h). That was followed by rapid skin healing and a favourable outcome for all patients, without significant adverse effects. These results suggested that IVIG could be an efficient treatment for SJS and TEN by substantially reducing the progress of the disease and the risk of death.

Based on individual age and the extent of detachment, the predicted number of deaths in this small group was no more than two. Studies including larger numbers of patients are obviously necessary to reach conclusions on the efficacy of IVIG.

Stella *et al.* [21] reported their experience with nine patients in a burns unit from Italy. Skin detachment was relatively limited, from 4 to 37%. One patient died, three needed mechanical ventilation and one needed haemodialysis. The progression of epidermal necrolysis stopped after an average of 4.8 days after the initiation of treatment.

In January 2003 Prins *et al.* [22••] reported a multicentre analysis of 48 TEN patients treated with IVIG. This was performed by the retrospective collection of patients in 14 centres, including a non-stated number of cases (15–20?) that had already been included in previous [5] or simultaneous publications [23••]. The patients were admitted a mean of 7 days after the onset of the disease. The skin detachment was above 10% of body surface (mean 44.8%; range 10–95%) at inclusion. IVIGs (eight different brands) were administered over 4 days, with a mean daily dose of 0.7 g/kg and a mean total dose of 2.7 g/kg (range 0.65–5.8 g/kg). Efficacy was judged on the cessation of the disease and the final outcome at 45 days. A rapid cessation of skin and mucosal detachment was observed (mean 2.3 days, range 1–6). Six deaths occurred (12%).

In the same issue of the *Archives of Dermatology*, Trent *et al.* [23••] reported their experience from the Department of Dermatology in Miami, USA. Sixteen consecutive patients with TEN and a surface of skin detachment ranging from 12 to 90% were treated with 1 g/kg of IVIGs per day for 4 days (brands not specified, at least two). Approximately half of these cases were simultaneously included in the multicentre report by Prins *et al.* [22••]. The efficacy of IVIG was evaluated by comparing the observed mortality with the mortality predicted by a validated prognosis score [24]. The cessation of the disease progression was also evaluated. The authors

observed a cessation of the disease in approximately 4 days. A validated prognosis score, 'SCORTEN', predicted six deaths and only one occurred. This dramatic, even if not statistically significant, result was interpreted as an 83% reduction in mortality as a result of IVIG.

A third paper from our team appeared in the same journal issue [25••]. It was a prospective non-comparative monocentre evaluation of the effect of IVIG therapy on the progression of the disease and mortality rate of patients with SJS and TEN. Thirty-four consecutive patients (nine with SJS, five with SJS–TEN and 20 with TEN) were treated a mean of 4.1 days after onset with 1 g/kg IVIGs for two consecutive days. One brand of IVIG (Tegeline, LFB laboratories, Les Ulis, France) was administered to 30 out of 34 patients. The doses were reduced for patients with decreased creatinine clearance. The mean area of skin detachment progressed from 19% of the body surface at inclusion to 32% after IVIG treatment. Epidermal detachment progressed in 22 patients, regressed in four, and did not change in seven. Patients hospitalized earlier than 4 days after the onset had a more important progression. This suggested that the spontaneous evolution was not altered by IVIG. Regrowth of the epidermis was obtained in 17 days. No improvement was seen in the mortality rate. The observed mortality rate was not significantly different (11 deaths, 32%) from what was predicted by the SCORTEN (eight deaths, 24%). Mortality was associated with a higher age, a classic observation in SJS and TEN, but also with impaired renal function at admission, suggesting a nephrotoxic effect of high-dose IVIG with sucrose, already documented in other situations [26,27]. Even though the number of patients was limited, these results were interpreted as excluding a strong benefit of IVIG on the mortality of SJS or TEN.

Two abstracts were presented at the 35th Annual Meeting of the American Burn Association in Miami Beach, 1–4 April 2003 [28,29]. The first compared 16 patients treated with IVIG (0.7 mg/kg a day for 4 days) and 16 were treated with supportive therapy. The two groups only differed by the earlier admission of those who received IVIG. IVIG did not produce any substantial improvement in outcome. The second compared 20 patients who did not receive IVIG with 23 treated with IVIG. The age, percentage of lesions and SCORTEN were initially similar. Mortality was 35% without IVIG and 48% with IVIG.

What can explain the discrepancies between these studies?

The results of the above studies differed slightly in the time needed for halting progression of the disease (2–4 days), the time to cicatrization (8.5–18 days) and the duration of hospital stay. The most striking clinical

differences between the reports by Prins *et al.* [22••] and by Bachot *et al.* [25••] concerned the outcome (13 versus 32% mortality, respectively) and side-effects of IVIG (none versus the frequent alteration of renal function).

The most frequently proposed explanations were: the utilization of different brands of IVIG, higher doses and earlier treatment in studies with positive results, the variable prevalence of HIV infection, and referral bias.

Use of different intravenous immunoglobulin brands

Analysis of different batches revealed significant batch-to-batch variations in the capacity of IVIG to inhibit Fas-mediated cell death *in vitro* [22••]. Many different brands and batches were used in each series, with the exception of the Créteil study [25••], in which 90% of patients received the same brand, and only one batch had been tested and confirmed to have an anti-fas activity. Prins *et al.* [22••] mentioned that they had tested the batches used in seven patients and found variable anti-fas activity but no obvious correlation with the clinical results. We therefore consider that these variations are not likely to explain the different results. Otherwise one should obtain an emergency test of anti-fas activity of each batch before treating a patient, an unrealistic requirement.

With the exception of the Miami group [23••], sucrose-containing IVIG preparations were most often used in the different studies. As the nephrotoxic potential of sucrose is established it is surprising that renal side-effects were observed only in the Bachot series [25••].

Different dosages

Prins *et al.* [22••] suggested that patients who responded to IVIG had received on average higher doses of IVIG. The mean total doses of IVIG were indeed higher in the study by Prins *et al.* [22••] than in the series by Bachot *et al.* [25••] (2.7 versus 2 g/kg, respectively). But the cases of Prins *et al.* [22••] received lower daily doses (0.7 versus 1 g/kg) for a longer period. That means that in both series patients had received exactly the same amount of IVIG after 3 days, a time at which the disease had stopped in one series and progressed in the other. It is therefore unlikely that a dose effect explained the 'specific' impact of IVIG on the progression of skin lesions. A dose relationship on mortality remains possible, but would be difficult to explain if dissociated from the effect on the skin.

Earlier treatment

Prins *et al.* [22••] suggested that in their series patients who responded to IVIG had received treatment earlier in the course of the disease. This was not clearly supported by their data, because the delay to hospitalization and treatment was not significantly shorter for patients who

survived compared with those who died. In addition, the mean time from the onset of disease to treatment was longer in their series than in the study of Bachot *et al.* [25••] (7.3 versus 4.1 days). Therefore earlier treatment does not appear to provide an appropriate explanation for the discrepancies within these series.

Inclusion and referral bias

In our opinion, such biases are probably an important cause of the reported differences. As a referral centre, Créteil may have included more severe patients, whereas the retrospective query of cases in many departments exposed Prins *et al.* [22••] to difficulties in case ascertainment and to the risk of a non-exhaustive collection in some centres.

Conclusion

The implication of the Fas/Fas ligand pathway is an important step in the mechanism of SJS and TEN. It remains unclear whether it is the only or even the most important pathway involved [30•]. The role of IVIG as pro or anti-apoptotic is not clear, particularly concerning activated cells.

To evaluate the future role of IVIG in the treatment of SJS or TEN a double-blind, placebo-controlled, randomized clinical trial would be necessary [30•]. It would necessitate a large number of patients. As an example, 400 patients should be included in such a trial to demonstrate a reduction in mortality from 23% (predicted in the series of Bachot *et al.* [25••] and Trent *et al.* [23••]) to 12% (observed in the series of Prins *et al.* [22••]).

Before designing such a large and very expensive trial it seems important: (1) to have a 'third party' look at the data gathered from the main published series; (2) to wait for the results obtained in France and Germany by the EuroSCAR surveillance network; and (3) to collect more *in-vitro* evidence on the effect of IVIG on the apoptosis of epidermal cells.

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