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Treatment of Epidermal Necrolysis with High-Dose Intravenous Immunoglobulins (IVIg)

Clinical Experience to Date

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Abstract

High-dose human intravenous immunoglobulins (IVIg) have now been used as a treatment for epidermal necrolysis for several years.

We have reviewed all series involving more than nine patients treated with high-dose IVIg for toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome (SJS) published in indexed journals. Nine series included a total of 156 patients; among the 156 reported cases, 32 patients died (20.5%). When the analysis was restricted to the five series that included some comparison with expected deaths, the mortality rate observed in patients treated with IVIg was 27% versus an expected rate of 30%. Because of high diversity in study designs and dosages of IVIg used, and because several series included duplicate cases, it was not possible to make more detailed statistical analyses, including individual prognostic factors and IVIg dosages.

In the absence of randomised controlled trials, this review does not provide a definite conclusion on the usefulness of IVIg in SJS or TEN; however, the analysis of published data does not suggest a dramatic efficacy.

We conclude that, in the absence of further studies, IVIg cannot yet be considered the standard of care for SJS or TEN.

Among severe skin reactions to drugs, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are the most life-threatening. TEN and SJS are closely related, and are both associated with the sloughing of the epidermis and mucous membrane erosions of the mouth, eyes and genitalia. The amount of sloughing epidermis is <10% of the body surface area (BSA) in SJS, whereas in TEN the skin detachment is usually >30% of the BSA and looks like a superficial burn. However, this is a schematic classification; overlapping cases may exist and are defined by an intermediate extent of the skin detachment.[1] Moreover, TEN, and less often SJS, may be associated with systemic involvement. In some cases, detachment of the bronchial mucosa leads to acute respiratory distress. Although rare, about two cases per million population per year,[2] these disorders are of great interest and concern for three main reasons: (i) high mortality (20–25%);[3] (ii) the pathophysiology of the dramatic death of epidermis, which is not fully elucidated; and (iii) the lack of a satisfactory treatment to improve disease outcome.

In TEN, as well as in burns, the extent of skin involvement has been shown to be an important

factor of mortality. However, many other parameters have also been identified. From the analyses of a large number of cases a prognosis score was constructed:[4] this severity of illness score for TEN (SCORTEN) includes, in addition to the percentage of BSA involved, six clinical or biological parameters that were proven to be independently related to the risk of dying. Thus, a patient's risk of dying is proportional to the given score. The usefulness of this SCORTEN has been confirmed by several groups[5-8] and would be an important tool for facilitating comparison of case series in clinical trials worldwide.

To date, there is no evidence-based treatment for these diseases. Many physicians use systemic corticosteroids or immunosuppressive drugs in addition to supportive therapy for halting the progression of the disease, which is believed to result from an immunological reaction.[3] Conversely, several experts considered these drugs to be harmful.[3]

1. Pathophysiological Mechanism

Up until now, the pathophysiological mechanism that leads to the dramatic death of keratinocytes and the subsequent systemic 'toxic effects' has not been fully elucidated. Pathological examination of the affected epithelium reveals widespread apoptosis of epidermal cells[9] and a moderate mononuclear cell infiltrate.

Lymphocytes present in the blister fluid at the site of skin lesions were recently demonstrated to be drug specific and to kill autologous keratinocytes.[10] These results strongly suggest that the mechanism of the disease is dependent on a drug-specific cell-mediated immunological reaction. The question of whether cytotoxic T lymphocytes explain the widespread apoptosis or need amplification mechanisms via a variety of cytokines remains controversial.

It has been suggested previously that the apoptosis of epidermal cells in TEN is related to upregulation of a protein called Fas ligand (FasL) on the membrane of keratinocytes. FasL interacts with the death receptor Fas (or CD95) that is present on the same cells.[11] Upon contact with adequate concentrations of FasL, cells expressing Fas rapidly undergo apoptosis. Such a mechanism has been suggested to explain several skin diseases, including lichen planus, contact dermatitis and others.

2. Rationale for Using High-Dose Intravenous Immunoglobulins (IVIg) in Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS)

2.1 IVIg and the Fas Ligand Theory

In vitro, high concentrations of normal human immunoglobulins inhibited Fas-FasL interaction and apoptosis of lymphocytes highly sensitive to Fas-mediated death. Immunoglobulins also inhibited keratinocyte apoptosis induced by high concentrations of recombinant FasL.[11] This effect was due to the blockade of the Fas receptor rather than to an interaction with FasL. The anti-Fas activity was variable with different batches of immunoglobulins.

On the basis of these *in vitro* findings, IVIg was administered in an open-label clinical trial to ten patients with SJS or TEN, all of whom survived. These preliminary results suggested that IVIg could be an efficient treatment for SJS or TEN, by substantially reducing the risk of death.[11]

2.2 Alteration of Immune Response

In addition to the possible blockade of FasL/Fas interaction, IVIg has been credited with many cell- or antibody-level effects on the immune response. IVIg had been used in many diseases mediated through an exaggerated immune response. A clinical benefit was demonstrated by randomised clinical trials in some diseases, including Kawasaki's disease, Guillain-Barré syndrome, idiopathic thrombocytopenic purpura and dermatomyositis.[12] These trials also provided information on administration and safety of IVIg. The total therapeutic dose was empirically set at 2 g/kg in 2- or 5-day infusions. The 2-day infusion was suggested to be more effective and equally well tolerated. Minor adverse effects (headache, fatigue, fever, nausea) occurred in no more than 10% of patients, and severe adverse effects (anaphylactic reactions, renal tubular necrosis) were rare.

2.3 Additional Expected Benefits from IVIg

IVIg is useful for the prevention of infection in patients with hypogammaglobulinaemia. It has been proposed that IVIg could also prevent severe infections in the intensive care setting; however, this has not been proven. Another potential effect could be participation in the correction of the severe loss of proteins that complicates TEN.[3]

3. Evaluation of Published Results of IVIg in SJS or TEN

We performed a systematic electronic search of PubMed. In the absence of any randomised clinical trials, this review included all nine series published in indexed journals that included at least nine patients. Because of the high risk of bias we did not analyse single case reports or very small series.

The nine series that were analysed are summarised in table I.[5-7,11,13-17] They comprised a total of 156 patients, of whom 22 had SJS and 134 had TEN or SJS/TEN overlap, treated in a variety of settings, with diverse and often unspecified brands of IVIg, and a variety of total doses and durations of treatment. Overall, the mortality rate was 20.5% (32 deaths). Thirty of 134 patients with TEN or SJS/TEN overlap died (22.4%).

In addition, we separately analysed studies that included at least some kind of control (either a retrospective series of patients treated in the same centre or death predicted by a validated prognosis score) and other series without controls. The first group consisted of five series[5-7,15,17] comprising a total of 100 patients. The observed number of deaths was 27 of 100 (27%), while the predicted/control numbers were 29 of 97 (30%). The second group consisted of 56 patients in four series[11,13,14,16] with no attempt to compare the results to some 'controls'. Only 5 of these 56 patients died (9%).

We also looked at whether the death rate was different in relation to the total doses of IVIg and the speed of initiation of treatment. The mean total doses were significantly different between published series ($p < 10^{-5}$; measured using H test, Kruskall Wallis). Five of six series with 'good results' (as defined by the author's conclusion that IVIg were effective) used total IVIg doses >2 g/kg bodyweight. The mean for these six series altogether was 2.7 g/kg. On the other hand, only one of three series with 'ineffective' results used >2 g/kg, with a mean of 2.0 g/kg for all three series together. In the latter of these three 'negative' series,[17] the authors had explored a possible dose effect: the mortality rates were 33% among patients who received >2.4 g/kg and 14% in patients who received less (a nonsignificant difference).

Concerning the time to initiation of treatment, the seven series that could be analysed (all but Trent et al.[5] and Campione et al.[6]) also differed significantly ($p = 0.03$; F statistics for comparison of means). In the four series with 'good results', the mean delay to initiation of therapy was 5.3 versus 5.9 days for series with negative findings, a nonsignificant difference.

4. Adverse Effects of IVIg in SJS and TEN

Only two of the nine series reported adverse effects related to IVIg treatment of patients with SJS or TEN. One series[7] reported a significantly higher incidence of complications in the group of patients who received IVIg than in controls; however, it was not specified whether these had been complications of TEN or of IVIg. Another series[15] reported an increase in plasma creatinine after IVIg infusion, which was more marked in elderly patients and in those with a history of impaired kidney function.

5. Discussion

The present review has several obvious limitations. A meta-analysis was not possible because none of the published series was a randomised controlled trial and because of substantial variability in the methodology of individual studies. Because some cases had been reported before in another series,[5,6,11] we decided to remove them from the series in which they were published for the second time.[14,16] We removed as 'duplicates' all cases easily recognised because of similar characteristics of age, gender, culprit drug, percentage of epidermal detachment and dose of IVIg; however, we may have missed a few other 'duplicates' when one or

Table I. Summary of nine published series from indexed journals on the use of intravenous immunoglobulin (IVIg) in patients with toxic epidermal necrolysis (TEN) or Stevens Johnson syndrome (SJS) which included at least nine patients

Study (year)	Type of study	Mean total dose of IVIg [g/kg] (duration [days])	Number of patients (disease)	Observed number of deaths (expected number)	Mortality (% of patients)	Time to treatment (days)	Authors' conclusion
Viard et al.[11] (1998)	Prospective, noncomparative	2.5 (4)	10 (SJS or TEN)	0	0	3.6	Effective
Stella et al.[13] (2001)	Prospective, noncomparative	2.8 (4)	9 (SJS or TEN)	1	11	6.1	Effective
Prins et al.[14][a] (2003)	Retrospective, multicentre	2.5 (4)	27[b] (TEN)	4	15[b]	6.1[b]	Effective
Bachot et al.[15] (2003)	Prospective, observed vs predicted death	1.9 (2)	34 (SJS or TEN)	11 (8.2 expected)	32	4.1	Ineffective
Trent et al.[5] (2003)	Prospective, observed vs predicted death	3.9 (4)	16 (TEN)	1 (5.8 expected)	6.2	3.5[c]	Effective
Prins et al.[16] (2003)	Retrospective, multicentre	2.4 (4)	10[d] (SJS)	0	0	4.3	Effective
Campione et al.[6] (2003)	Prospective, observed vs predicted death	2 (5)	10 (TEN)	1 (3.2 expected)	10	ND	Effective
Brown et al.[7] (2004)	Prospective, historical controls	1.6 (4)	24 (TEN)	10	41.7	9.2	Ineffective
Shortt et al.[17] (2004)	Prospective, historical controls	2.8 (4)	16 (TEN)	4	25	4.8	Ineffective

a This retrospective multicentre series included eight cases already published in Viard et al.,[11] nine cases included in Trent et al.[5] and at least four included in Campione et al.[6]

b Recalculated from published data after removal of cases identified as duplicates.

c Probably erroneous value. Individual data presented in Prins et al.[16] for 9 of these16 patients are not compatible with a mean of 3.5 days and suggest that the actual mean should be at least 8 days.

d This retrospective multicentre series included two cases already published in Viard et al.[11]

ND = no data available.

more characteristics were reported differently from one paper to another. We are also aware that such a compilation of uncontrolled data could overestimate the possible benefit of IVIg because of publication or other bias.

With these limitations in mind, we concluded that this evaluation of nine series does not suggest a strong benefit from IVIg in SJS or TEN for the following reasons.

At first glance the mortality rate of 20.5% among the 156 patients treated by IVIg does not appear very different from the 20–25% generally quoted.[3] If we return to the 134 patients with TEN or SJS/TEN overlap, the results seem better if one compares the observed mortality rate of 22.4% with the 30% generally quoted.[3] However, this overall death rate was actually a mixture of a very low mortality in some series and a much higher mortality in others. Several factors could have contributed to the observed differences, including the experience level of the centre, design of the study, earlier or later timing of intervention, and brands and doses of immunoglobulins used. Some of these factors could not be analysed because of a lack of information in the individual reports.

The delay between onset of disease and the initiation of IVIg was analysed. It is certainly an important factor influencing the outcome of epidermal necrolysis because it implies the removal of all suspected drugs, the correction of organ impairment and fluid replacement. In patients with a delay in initiation of IVIg >10 days, the efficacy of IVIg may be questioned as the evolution of the disease generally stops at this point regardless of treatment. Regardless of whether the results were considered positive or negative, the time to treatment did not appear to differ between centres.

The total doses of IVIg administered were definitely higher in centres with better results. However, it was not possible to investigate whether this relationship was causal as that would require a multivariate analysis integrating individual doses and prognosis factors, and eliminating duplicate cases. These pieces of information were often missing, making it impossible to confirm the prior suggestion by Prins et al.[14] that patients who received higher doses of IVIg had a better outcome. Therefore, to date, there is no good evidence that IVIg dosage could influence the outcome of TEN.

Finally, when we selected the five series where authors introduced some comparison (expected death rate according to SCORTEN and/or historical controls from the same centre) the observed mortality rate (27%) was very close to the 'control' mortality (30%). Interestingly, all five centres had significant prior experience with the management of patients with SJS or TEN.

6. Recommendations to Clinicians

To date, definite conclusions concerning the efficacy of IVIg compared with standard care in a specialised unit cannot be made. However, from this analysis of published series, it does appear that treatment with IVIg is not the 'magic bullet' that will dramatically improve the prognosis for SJS or TEN.

Prior to more data being available, including a randomised controlled trial, if feasible, what are the practical implications of these results? Some clinicians consider that, in the absence of evidence of effectiveness, there is no reason to prescribe an expensive treatment. Others will argue that any chance of a benefit should be explored in the absence of major risks. If this option is chosen, only preparations without sucrose and without any risk to the kidney should be used.

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