Intravenous Immunoglobulin Treatment for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

A Prospective Noncomparative Study Showing No Benefit on Mortality or Progression

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Background: It has been proposed that Fas–Fas ligand interaction was responsible for the apoptosis of epidermal cells in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) and that high doses of intravenous immunoglobulin (IVIG) could help patients by blocking the apoptosis.

Objective: To study the effects of IVIG on SJS and TEN.

Design: Prospective open trial.

Setting: Referral center of a university hospital.

Patients: Thirty-four consecutive patients admitted for SJS (n=9), SJS-TEN (n=5), or TEN (n=20) a mean of 4.3 days after onset.

Intervention: A dose of 2 g/kg of IVIG was administered within 2 days (half doses or full doses over a longer period for patients with low creatinine clearance).

Main Outcome Measures: Detached plus detachable proportions of the total body surface area measured before and after treatment and predicted death rate estimated on admission with a validated prognostic score.

Results: Epidermal detachment involved a mean±SD 19%±16% of the total body surface area on admission and 32%±26% after IVIG treatment (progression in 22 of 34 cases, including most patients referred early). The prognostic score predicted 8.2 deaths (24%); 11 were observed (32%; 95% confidence interval, 17%-51%). Most deaths occurred in elderly patients who had initially impaired renal function.

Conclusions: The confidence interval of the observed death rate excludes a dramatic decrease in mortality. No measurable effect was observed on the progression of detachment or on the speed of reepidermalization. These results do not support the routine use of IVIG treatment for patients with SJS or TEN, especially in cases of impaired renal function.

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TOXIC EPIDERMAL necrolysis (TEN) and Stevens-Johnson syndrome (SJS) are severe skin reactions, usually to drugs, associated with a widespread destruction of the epidermis. The 2 diseases are closely related: SJS is a limited form characterized by mucous membrane erosions and blisters on limited areas of the skin (<10% of the total body surface area [TBSA]); TEN resembles superficial burns because of the confluence of blisters and erosions on more than 30% of the TBSA. Overlapping cases are defined by an intermediate extent of the skin lesions. These diseases are rare (1.5-2 cases per million population per year) but very severe, with an overall mortality of 20% to 25% and frequent disability in survivors.1

There is no common treatment for these diseases. Many physicians use systemic corticosteroids or immunosuppressive drugs in addition to supportive therapy to halt the progression of these diseases, which are believed to result from an immunologic reaction, while others consider these drugs to be harmful.1

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Evidence for a possible effective treatment of TEN with intravenous immunoglobulin (IVIG) came from laboratory data demonstrating that the sudden and widespread apoptosis of epidermal cells in TEN is related to up-regulation of a protein called Fas ligand (FasL) on the membrane of keratinocytes.2 The FasL interacts with the death receptor (Fas or CD95) present on the same cells. On contact with FasL, cells expressing Fas rapidly undergo apoptosis.2,3 High concentrations of normal human immunoglobulin inhibit
Fas-FasL interaction and apoptosis through an anti-Fas activity. In addition, IVIG treatment was used in an open study with 10 patients with SJS or TEN who all survived. The progression of the skin lesions was rapidly interrupted after IVIG infusion (within 24-48 hours), accompanied by rapid skin healing (7 days as a mean) and without significant adverse effects.

These preliminary results suggested that IVIG could be an efficient treatment for SJS or TEN by substantially reducing the progress of the disease and the risk of death. However, a small series is of limited value, and the results should be confirmed by an appropriately designed randomized clinical trial. Large numbers of patients would be necessary. As an example, we calculated that 400 patients should be included in such a trial to demonstrate a reduction in mortality from the current 23% to 12%. While we were exploring the feasibility and ethics of a double-blind, placebo-controlled randomized trial of IVIG therapy, we conducted the present monocenter pilot trial, a prospective noncomparative evaluation of the effect of IVIG therapy on the progression of the disease and mortality rate of patients with SJS and TEN.

METHODS

PATIENTS

All consecutive patients hospitalized in our intensive care unit with SJS or TEN from January 1999 to December 2000 were treated with IVIG when they fulfilled the following inclusion criteria: (1) detachment of epidermis on more than 1% of their TBSA; (2) disease progression within the 24 hours preceding admission; (3) no contraindication to the use of IVIG (ie, creatinine clearance <20 mL/min [<0.33 mL/s], according to the Cockcroft-Gault formula, or a history of anaphylactic response to immunoglobulins); and (4) diagnosis of SJS and TEN confirmed by skin biopsy specimen analysis showing full-thickness necrosis of the epidermis and by review of clinical photographs by an external international group of experts. Among 38 patients admitted for SJS or TEN, 3 were not included: 2 because of no progression of the disease before hospitalization and 1 because of terminal renal failure. A total of 35 patients fulfilled the inclusion criteria, but 1 of these was not treated because of insufficient peripheral venous access and disease severity insufficient to justify the risk of a central line.

TREATMENT

A total dose of 2 g/kg of IVIG was administered by continuous infusion initiated immediately after admission. This was done within 2 days for patients with normal renal function (1 g/kg per day). Full doses over a longer period or half doses were administered to patients with creatinine clearance of 60 mL/min (1.0 mL/s) or slower (the initial rate of 0.4 g/kg per day was increased if renal function improved). In emergency situations, IgA level determination was not possible.

Three different brands of IVIG were used, depending on availability at the hospital pharmacy. Thirty patients were treated with Tegeline (Laboratoire français du Fractionnement et des Biotechnologies, Les Ulis, France), 2 with Sandoglobulines (Novartis pharma SA, Rueil-Malmaison, France) (patients 1 and 2), and 2 with Gammagard (Baxter SA, Maurepas, France) (patients 32 and 34). Each patient received a single brand. Only Gammagard did not include sucrose.

No other drug considered active on SJS or TEN was administered, especially no corticosteroid or immunosuppressive agent. Symptoms were treated as needed with infusion of crystalloids, enteral nutrition, topical antiseptics, air suspension bed (KinAir; Kinetic Concepts Inc [KCI], San Antonio, Tex), warming, and systemic antibiotics according to our usual protocol. The IVIG was included within the total volume of fluid administered to avoid fluid overload.

EVALUATION OF EFFECT

A prognosis score (SCORTEN) was calculated at admission for each patient. This SCORTEN had been validated at our institution for its good accuracy in predicting the risk of dying from SJS or TEN. This score is calculated by giving 1 point for each of 7 clinical variables evaluated during the first 24 hours: patient older than 40 years, malignancy, heart rate higher than 120 beats per minute, initial percentage of epidermal detachment higher than 10%, serum urea level higher than 28 mg/dL (10 mmol/L), serum glucose level above 252 mg/dl (14 mmol/L), and bicarbonate value below 20 mEq/L. The probability of dying predicted by the score is 0.03 for a score of 0 or 1 point, 0.12 for 2, 0.33 for 3, 0.58 for 4, and 0.90 for 5 to 7. The actual death rate was compared with the predicted one.

As shown in the Table, the 34 treated patients includes 22 women and 12 men, with mean ± SD age of 47 ± 21 years. Nine (26%) had a diagnosis of SJS, 20 (59%) of TEN, and 5 (15%) of SJS-TEN overlap. Twelve (35%) had acquired immunodeficiency syndrome (AIDS). Drugs considered to have induced the disease were nevirapine (7), carbamazepine (5), cotrimoxazole (3), phenobarbital (2), allopurinol (2), antituberculous agents (2), sulfadoxine (1), sulfadiazine (1), pristinamycine (1), omeprazole (1), thiabendazole (1), amoxicillin (1), sulindac (1), ibuprofen (1), and undetermined (5).

Patients were admitted a mean ± SD of 4.1 ± 2 days after the first sign of the reaction (range, 1-9 days; median, 4 days). All had erosions of mucous membranes at several sites and detached or detachable epidermis on 19% ± 16% of the TBSA at admission. The total dose of IVIG actually administered was 1 g/kg for 3 patients (in 2 cases because of initial renal failure and in 1 because of rapid progression of disease after the first infusions) and 2 g/kg for 31. In 27 cases, the IVIG was infused over 2 days; in 7 cases over 3 to 5 days. We observed no reaction to the infusion of IVIG.

The SCORTEN predicted 8.2 deaths (21%) in this series, while 11 (32%) actually occurred (95% confidence interval, 17%-51%) a mean ± SD of 10 ± 8 days after hospitalization, mostly from septic shock. The excess of mortality was observed mostly in patients older than 70 years (7 deaths vs 3 predicted; P = .12). In patients younger than 70 years, 4 deaths were observed when
were predicted. Patients hospitalized earlier than 4 days after onset (12 patients) had a predicted mortality of 3; 4 deaths occurred. One patient died before day 3. Among 12 patients with AIDS, 2 (17%) died. The principal causes of death overall were sepsis, pulmonary failure, and multiple organ failure.

At day 3, detached and detachable areas involved a mean±SD of 32%±26% of the TBSA (ie, a progression of 12.4%±15.7% since admission). Epidermal detachment progressed in 22 patients, regressed in 4, and did not change in 7. Patients hospitalized earlier than 4 days after onset had a lower extent of detachment on admission than patients admitted later (10%±9.5% vs 23%±16%), but at day 3 after admission the extent was not statistically different (27%±24% vs 34%±27%). Indeed, patients hospitalized earlier than 4 days after the onset had a more important progression (17%±17% vs 10%±15%). In survivors at day 11, detached and detachable area involved 17%±17% of TBSA, and healing was observed 18±16 days after admission. Three patients had ocular sequelae at discharge.

The mean±SD serum creatinine level increased from 1.1±0.4 mg/dL (93±37 µmol/L) to 1.1±0.4 mg/dL (113±105 µmol/L) at day 3. Initial creatinine clearance of 50 mL/min (0.8 mL/s) was associated with a very poor prognosis (6 deaths among 7 patients vs 5 of 27 patients with higher creatinine clearance; *P* = .002). Six of these patients with poor renal function were older than 70 years, and in this subgroup the SCORTEN predicted 3.4 deaths. For the 27 patients with creatinine clearance above 50 mL/min (0.8 mL/s), the SCORTEN predicted 4.7 deaths, and 5 occurred.

**COMMENT**

Stevens-Johnson syndrome and TEN are drug-induced diseases associated with a high morbidity and mortality and have no established treatment. The recent sugges-
tion that IVIG could block the process raised high hopes. The present report is the largest open trial from a single center of patients with SJS and/or TEN treated by IVIG and evaluated by an experienced team using strict and validated criteria. The results of this series are very disappointing. The death rate (32%) was not significantly different from what was predicted in these patients (24%) by a validated prognosis score and showed no trend toward improvement. It was also higher than the historical death rate in our center (ie, 20%). Even though the number of patients was small, the present findings strongly suggest that the expectation of a strong benefit of IVIG on the mortality of SJS or TEN is not realistic.

One may argue that working through a referral center, we had to deal with more severe cases than are seen in usual practice, especially in patients with associated diseases such as AIDS. This is probably true, but the overall predicted and observed mortality rates were in the usual range and were even slightly higher than the rates predicted by SCORTEN, a validated prognostic scoring system. In addition, as has been reported elsewhere, the severity and mortality of TEN in our patients with AIDS were not higher than in other cases.

As is often the case with SJS or TEN, many patients had underlying diseases that contributed to the severity of the drug reaction and to the high death rate. This is taken into account by the SCORTEN system. Excluding all patients with any risk factor would decrease the expected death rate to near 0 and would create an artificial impression that IVIG treatment is beneficial to survival.

We did not observe the arrest in progression of skin lesions that was expected from the apoptosis-blocking effect of IVIG. Because patients were admitted a median of 4 days after the onset of the disease, we wondered whether the therapy was not initiated too late. In the subgroup of patients hospitalized and treated earlier than 4 days after onset, the destruction of epidermis progressed to an even greater extent than in patients treated later. This suggests that the spontaneous evolution was not altered by IVIG.

Regrowth of the epidermis occurred in a time frame similar to our prior experiences (17 days). However, we observed a decrease in renal function after treatment that contrasted with our prior experience of an early improvement in renal function after correction of hydroelectrolytic disturbances. This strongly suggests a nephrotic effect of high-dose IVIG in patients with compromised kidney perfusion, an adverse effect of IVIG therapy that has already been documented. Nephrotic effects were principally attributed to the sucrose-based preparations used in 32 of our 34 patients, as in the original series. We cannot exclude the possibility that this nephrotic effect contributed to the death of 2 of the 12 patients with initial detachment of less than 5%. The discrepancies between the present results and those of prior case reports and short series are probably explained by the selection of patients with different spontaneous prognosis, especially if patients with risk factors had been excluded from other series.

One may wonder whether higher doses could have a better effect. In the study by Viard et al, IVIG therapy was administered over 4 days with a daily dose of 0.2 to 0.75 g/kg. A positive response was observed in 1 or 2 days, after a total dose of at most 1.5 g/kg. During the same time frame in the present study, 24 of our 34 patients had already received higher doses. One may also consider the hypothesis that IVIG of different origins and preparations might have different effects. However, this has never been suspected in any of the diseases where IVIG therapy had a definite efficacy. Furthermore, it is not possible to test every IVIG batch for anti-Fas activity before emergency use.

Our negative results may indicate that the destruction of epidermal cells is provoked by the simultaneous activation of several apoptosis pathways and that blocking the Fas receptor by IVIG therapy is not enough to effect a cure. Our observations are not compatible with the huge reduction in death rate that we expected from high-dose IVIG treatment for patients with SJS or TEN. They are compatible with a weak benefit on mortality, principally in younger patients, but even this is unlikely because we observed no effect on the progression of epidermolysis, the proposed target of IVIG. A controlled trial with more than 1000 patients to demonstrate a decrease in mortality from 21% to 17% is probably not feasible in this rare disease. Practically, IVIG treatment cannot be recommended as a treatment of SJS and TEN without further studies, and its use should be discouraged in elderly patients and in patients with impaired renal function.

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