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CLINICAL REPORT

High-dose Intravenous Immunoglobulin for Severe Drug Reactions: Efficacy in Toxic Epidermal Necrolysis

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High-dose intravenous immunoglobulin has been proposed as an alternative treatment for several immuno-mediated inflammatory skin diseases, usually at a dosage of 1–2 g/kg. We describe the treatment of 10 patients affected by toxic epidermal necrolysis using 400 mg/kg per day on 5 consecutive days – a schedule that is lower than previously reported schedules. According to the SCORTEN, the earlier predicted mortality rate was 35%. After high-dose intravenous immunoglobulin therapy, a mortality rate of 10% and a survival rate of 90% were reached. In particular, nine patients showed a dramatic improvement already after one course of infusion started at an early stage of the disease. It is our experience, and that of others, that high-dose intravenous immunoglobulin can be considered the drug of first choice for toxic epidermal necrolysis, one of the most severe life-threatening dermatological conditions, and a valid alternative therapy for different long-standing chronic dermatological diseases. This therapy can also be effective in avoiding high steroid dosages and consequently steroid-related or immunosuppressive-related side effects. It is therefore reasonable to propose high-dose intravenous immunoglobulin treatment as a valuable therapeutic tool for dermatologists. ***Key words: high-dose intravenous immunoglobulin; toxic epidermal necrolysis.***

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High-dose intravenous immunoglobulins (IVIGs) contain over 90% monomeric IgG and small amounts of IgA, IgM and possibly IgE (1). Several immunomodulatory effects are proposed to explain their therapeutic effects mostly by fas-mediated apoptosis (2) and by anti-inflammatory action due to the constant fragment (Fc) of Ig (3, 4). The list of dermatological conditions treated with IVIG is gradually increasing (1, 5). Toxic epidermal necrolysis (TEN), autoimmune diseases (dermatomyositis, systemic lupus erythematosus, cutaneous lupus erythematosus, systemic sclerosis), blistering autoimmune diseases (pemphigus vulgaris, bullous pemphigoid, herpes gestationis, epidermolysis bullosa acquisita, linear IgA bullous dermatosis), pyoderma gangrenosum, atopic dermatitis, chronic autoimmune urticaria and Kawasaki's syndrome have all been tested with dosages ranging from 1 to 3 g/kg per cycle (2, 5–7). We present the positive therapeutical results obtained using IVIG infusion at a lower dosage of 400 mg/kg in 10 patients affected by toxic epidermal necrolysis, the most severe life-threatening cutaneous drug reaction.

PATIENTS AND METHODS

Ten patients (8 females and 2 males) affected by TEN, ranging from 21 to 95 years of age (see Table I), were observed in our department, one of the main burns-unit centres in central-southern Italy, and enclosed in the present study. The patients were hospitalized in the period 1998–2002. In all patients, the diagnosis was made according to the Stevens-Johnson syndrome (SJS) and TEN classification (8) and confirmed by histological examination. Moreover, each case was evaluated and confirmed by a EuroSCAR consensus (Severe Cutaneous Adverse Drug Reactions) (9).

A mean total body surface area detachment (TBSA) of 44% was counted and the following clinical parameters for each patient were collected: age, sex, biopsy punch, % TBSA (according to the rule of nine for burns patients) (10), mucosal involvement, causative drugs and the time of their dismission. In addition, heart rate, concurrent malignancies, serum urea, bicarbonate and glucose levels were all considered to calculate the SCORTEN (11) (Table I). The following drugs could be considered as causative agents: acetaminophen, acetylsalicylic acid, pirantel-pamoato, ketoprofene, luminale, mesulid, phenobarbital and two unidentified non-steroidal anti-inflammatory drugs.

IVIG therapy was started within 3 days from the onset of TEN. The presenting clinical signs, detected in 8 patients, started with a flu-like syndrome and widespread macules (spot lesions), blisters and flat atypical targets eruption, typically located on the face and trunk, leading, in 24–48 h, to large areas of epidermal detachment. In two patients, only epidermal detachment, without macules or target lesions, was observed. IVIG infusion, 400 mg kg^{-1} day^{-1} for 5 consecutive days, was given to all patients demonstrating TEN syndrome. In addition, wide range antibiotic therapy, in order to prevent infections, and granulocytic-monocytic stimulating factor (GM-CSF), 300 μg day^{-1}, in cases indicative of severe neutropenia, were prescribed. The SCORTEN was calculated at the initial administering and at the end of IVIG infusion, day 5 (Table I).

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Table I. *Presenting clinical parameters and outcomes of our series of patients treated with IVIG infusion*

Sex/age	Flat atypical targets	Macules with or without blisters	TBSA (%)	Causative drugs	SCORTEN	Outcome
F/20	Yes	Yes	70	Aspirin	3	Healed
F/21	No	Yes	60	Pirantel-pamoato	4	Healed
F/95	No	Yes	70	Ketoprofene	4	Healed
F/85	Yes	Yes	65	Not identified	4	Healed
F/44	Yes	Yes	30	Luminale	2	Healed
M/75	No	No	15	Fenobarbital	2	Dead
M/40	No	No	15	Diclofenac	2	Healed
F/12	No	Yes	40	Not identified	2	Healed
F/24	Yes	Yes	40	Mesulid	1	Healed
F/70	No	Yes	80	Aspirin	4	Healed

TBSA = Total body surface area detachment; SCORTEN: Severity of illness for TEN; IVIGs: intravenous immunoglobulins

RESULTS

The efficacy of the treatment was evaluated according to the following data: arrest of further epidermal or mucosal detachment, time in days necessary to obtain the clinical response, final outcome at 40–45 days (deceased or alive), sequelae, such as cutaneous hyperpigmentation, symblefaron, nail dystrophies, underlying diseases (if present), tolerability to IVIG. Within 48 h from the first infusion, IVIG therapy was effective in 9 patients, independently of their initial TBSA, either in arresting the skin detachment or in demonstrating a dramatic improvement of the vital parameters. Complete re-epithelization was reached between days 25 and 40, depending on the initial TBSA. Headache, nausea and gastrointestinal tract disturbances were the side effects detectable in 2 out of 10 patients. One patient with a past history of severe ischaemic cardiopathy died as a result of cardiac arrest during the first day of infusion.

DISCUSSION

Several immunomodulatory effects have been proposed to explain the therapeutic efficacy of IVIG (12). TEN is an extremely severe skin disease associated with a mortality rate of approximately 30%, with a possible increase to an average of 50% in elderly patients. Earlier mortality rate of patients with TEN in our department was 35% and 58.3%, respectively (EC et al; unpublished observation). Drugs such as cyclosporin A, cyclophosphamide, plasmapheresis and N-acetylcysteine have currently been proposed for the treatment of TEN (13–16), including the use of corticosteroid, which remains controversial (17, 18). The induction of extensive keratinocyte apoptosis is now considered to be the main key feature of the pathogenesis. Therapeutic modalities capable of inhibiting apoptosis are therefore likely to be useful in the early phase of TEN (2, 19). Keratinocytes normally express cell-death receptor Fas (CD95) and low levels of its ligand, while TEN keratinocytes express high levels of lytically active Fas ligand. Anti-Fas antibodies, present in IVIG, potently block Fas-mediated keratinocytes apoptosis, therefore inhibiting the progression of TEN (2, 19, 20). Because of this mechanism it is worthwhile to begin the infusions in the earliest possible phase of TEN.

Through the use of IVIG therapy, at a dosage of 400 mg/kg/day, we were able to reach, in our series, a survival rate of 90%. The patient who died as a result of cardiac arrest was already suffering from ischaemic cardiopathy; an association between IVIG administration and cardiac or cerebral ischaemia in older individuals has been reported (21), but the sudden occurrence of the extreme severe cutaneous condition authorized the use of IVIG. The absence of severe side effects, such as headache, nausea and gastrointestinal tract disturbances, may be related to the relatively low dosage of IVIG administered.

In conclusion, in our experience and in that of others, including a recent multicentre trial (22), IVIG can be confirmed as a first choice treatment of TEN. IVIG can be prescribed to avoid high steroid dosages and consequently steroid-related or immunosuppressive-related side effects. In addition, our results suggest that the dosage of 400 mg/kg is at least as effective as higher dosages, as well as demonstrating a higher tolerability.

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