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Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS): Experience with high-dose intravenous immunoglobulins and topical conservative approach A retrospective analysis

Maurizio Stella [a,*], *Alessandra Clemente* [a], *Daniele Bollero* [a], *Daniela Risso* [a], *Paola Dalmasso* [b]

[a] *Department of Plastic Surgery and Burn Centre, CTO Hospital, Via Zuretti 29, 10126 Torino, Italy*
[b] *Department of Public Health and Microbiology, University of Torino, Italy*

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ABSTRACT

Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) are rare, drug-induced, severe acute exfoliative skin and mucosal disorders.

Several treatments previously proposed have produced contradictory results in small series; in 1998 the use of intravenous immunoglobulins (IVIG) was introduced with excellent clinical findings.

Our experience (1999–2005) using IVIG in the therapy of TEN/SJS, together with a local conservative approach, is reported and related to our previous treatments (1993–1998). The SCORTEN and the standardized mortality ratio (SMR) was used to evaluate the efficacy of our therapeutic modalities.

Eight patients were treated before IVIG era and 23 patients have been treated with IVIG. There was no significant difference in SCORTEN between the two groups. Concerning the local approach, a conservative wound management in IVIG series replaced an extensive epidermal debridment and coverage with artificial skin substitutes of the pre-IVIG series. Overall mortality in patients treated before IVIG was 75% (6/8), in the IVIG group it decreased to 26% (6/23) with a cessation of further epidermal detachment after an average of 5 days (3–10 days) from the onset of the therapy. The SMR showed a trend to lower actual mortality (not significative) with IVIG treatment than the predicted mortality (SMR = 0.728; 95% CI: 0.327–1.620).

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1. Introduction

Toxic epidermal necrolysis (TEN) is an acute life-threatening exfoliative drug-induced skin pathology, having a clinical picture similar to extensive partial-thickness burns [1]. On this basis, burn units have been recently considered the ideal place for the management of TEN patients. Almost all the patients with TEN present associate mucosal lesions, including ubiquitous painful erosions and crusts [2].

About physiopathology, recently it has been demonstrated that TEN is due to alterations in the control of keratinocites apoptosis [3,4] mediated by interaction between the cell-surface death receptor Fas and its ligand (Fas ligand: FasL or

* *Corresponding author*. Tel.: +39 011 6933435; fax: +39 011 6933425.
E-mail address: stella.maurizio@libero.it (M. Stella).
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CD95L) [5]; up-regulation of keratinocyte FasL expression is the trigger for keratinocyte destruction during TEN [6].

More than 100 different drugs have been advocated as causes of TEN [7] but no skin or in vitro tests are actually available to demonstrate a clear correlation between TEN and the culprit drug and, at the same time, animal models are lacking.

Correlation between the illness and the drug intake is based on the recognition that TEN usually develops 1–3 weeks after administration of the offending drug [8]. Indeed a clear identification of the responsible drug is often presumptive, because there are several confounding factors frequently involved: for instance the frequent concomitant use of multiple different drug therapies.

Clinical diagnosis is based first on the presence of characteristic eruptions of erythematous confluent maculae together with positive Nikolsky's sign (dislodgement of epidermis by lateral pressure). Skin biopsy shows a typical histomorphological picture of full-thickness epidermal necrosis with an only slightly altered underlying dermis. Immunohistochemistry confirms the clinical diagnosis excluding other cutaneous diseases (like blistered pemphigoid or drug-induced linear immunoglobulin A blistered disease or acute generalized exanthematous pustolosis) that clinically can mimic TEN [9,10].

TEN incidence, in different national studies, has been estimated to be approximately 0.5–1.89 cases per one million people per year [11], 2.7 times higher among elderly than younger adults [12], probably due to a greater pharmaceutical use. Moreover, incidence in people with human immunodeficiency virus is much higher (0.01–0.1%) [13]. The mortality rate associated with TEN varies widely between the studies, ranging from 20% to 75% [14].

Treatment is based on the early removal of the suspected drug [15,16]. Other associated clinical approaches include local management, fluid replacement, nutritional support and systemic treatments that aim to stop the progression of the skin disease. About local management some authors suggest to treat the wounds with the conservative method [6,17], others with a more aggressive approach by means of mechanical debridement and coverage with skin substitutes [18,19], including biological skin covers (auto-grafts, xenografts, cultured keratinocites, glycerol-preserved skin allografts [20]).

Concerning systemic treatments, high-dose corticosteroid therapy has been widely employed [21–24] with uncertain results; recently other treatments (granulocyte colony stimulating factor [25,26], cyclophosphamide [27], cyclosporin [19,28], plasmapheresis [29,30], N-acetylcysteine [31], anti-tumour necrosis factor-α antibodies [32] and ulinastatin [33]) have been attempted. Moreover, patients included in the cited series are few.

In 1998, on the basis of the identification of the mechanism of keratinocytes apoptosis [6] in SJS and TEN, a therapy based on the use of intravenous immunoglobulins (IVIG) was proposed with excellent results. It was demonstrated that IVIG have the capacity to inhibit Fas–Fas ligand-mediated apoptosis. Therapeutic effect of immunoglobulins is likely to involve inhibition of Fas-mediated keratinocyte death by naturally occurring Fas-blocking antibodies contained within human immunoglobulins preparations [6], acting directly on the Fas–Fas ligand system at the keratinocytes surface [34]. Other case-reports as in adults as in children successfully treated with IVIG have been published [11,35–38].

In this article it is reported our experience (1999–2005) using IVIG and conservative local approach in the treatment of TEN in comparison to our previous treatments (1993–1998), evaluating the complications occurred and the survival rate according to a TEN-specific severity of illness scale (SCORTEN) [39–41].

SCORTEN is calculated by giving 1 point for each of 7 independent risk factors (age $>$ 40 years, presence of malignancy, body surface area involved $>$ 10%, serum urea nitrogen level $>$ 28 mg/dL, glucose level $>$ 252 mg/dL, bicarbonate (HCO_3) level $<$ 20 mequiv./L, and heart rate $>$ 120 beats/min) evaluated during the first 24 h of admission. The predicted mortality percentage is then based on the number of risk factors that each patient possesses. Patients with 0–1 risk factors have an expected mortality rate of 3.2%, 2 risk factors 12.1%, 3 risk factors 35.3%, 4 risk factors 58.3%, and 5 or more risk factors 90%.

2. Patients and methods

2.1. *Patients 1993–1998*

All hospitalized patients to the Turin Burn Center with a diagnosis of SJS or TEN from January 1993 to January 1998 were included in this series. Diagnosis was made by dermatologists and confirmed by histopathological examination. In this period patients were primary admitted to a dermatological unit and transferred to the burn center only when their general clinical conditions were judged critical.

No specific pharmacological protocol was at that time used: six out of eight received corticosteroids, one low-dose immunoglobulins and one corticosteroids and immunoglobulins (Table 1). Treatments included also low molecular weight heparin, H_2 antihistamines and antibiotic prophylaxis.

Fluid requirement was estimated with Parkland formula and administered as lactated Ringer's solution, using in all patients central venous catheter. Regarding nutrition five patients were feeded parenterally, one received entero-parenteral nutrition and one an increased oral intake. The caloric support was calculated, as in burn patients, according to Curreri formula [42].

Wound management was aggressive, based on extensive epidermal debridment and coverage of the denuded dermis with artificial skin substitutes (see Table 1).

For each patient the following clinical parameters were recorded and analyzed: age, sex, TBSA percentage of detached skin, presence or absence of mucosal involvement, previous diseases and putative causal drugs, interval from onset to burn unit admission, time to response and to complete skin healing, length of hospital stay, complications and outcome (Table 1).

SCORTEN was calculated on the basis of the seven clinical variables evaluated during the first 24 h of admission and the observed mortality compared with the predicted one.

2.2. *Patients 1999–2005*

All patients admitted to the our Burn Center between 1999 and 2005 with a diagnosis of SJS or TEN were included in this series. Diagnosis, as before, was made by dermatologists in the

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