SHORT COMMUNICATION

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Analytical quantification of the inflammatory cell infiltrate and CD95R expression during treatment of drug-induced toxic epidermal necrolysis

Abstract The treatment of drug-induced toxic epidermal necrolysis (TEN) remains unsatisfactory. Intravenous immunoglobulins (IVIg) and intravenous cyclosporin A (CsA) have shown some efficacy in short series of patients. We assessed the effects of IVIg and CsA on TEN lesional and apparently uninvolved skin using standard histology and immunohistochemistry. Cutaneous biopsies were taken from necrotic and clinically uninvolved TEN skin at admission (D1) before any treatment, and after a 5-day treatment (D5). Two IVIg-treated patients (0.75 g/kg/day), two CsA-treated patients (5 mg/kg/day) and two control patients only receiving supportive care were compared. Biopsies were examined by standard histology and immunohistochemistry using antibodies directed to CD68 antigen (macrophages), CD45R0 antigen (activated T lymphocytes), Factor XIIIa (dermal dendrocytes) and the CD95 receptor (apoptosis marker). The different cell densities were evaluated by computerized image analysis. The clinical outcomes with the different treatments were also recorded. There was no obvious difference in the duration of hospitalization in intensive care unit between the three groups but one patient passed away in each of the IVIg- and CsA-groups. At D5, no differences were found between the three groups in the histological and clinical rate of re-epithelialization, and in the evolution of T lymphocyte, macrophage and dendrocyte densities in the epidermis and dermis. However, the expression of the CD95 receptor was similarly and strongly abated at D5 in the epidermis of IVIg- and CsA-treated patients, while it was conversely increased in the two patients under supportive care only. Such a difference was found both in necrotic and uninvolved sites. IVIg and CsA treatments thus appeared to exert no obvious effect on the inflammatory infiltrate, but both abated the expression of the CD95 receptor in the skin of TEN patients. This effect did not seem sufficient to fully reverse the clinical evolution of the disease. It is inferred that IVIg and CsA do not completely abate the TEN process.

Keywords Toxic epidermal necrolysis · Cyclosporin A · Immunoglobulin

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Drug-induced toxic epidermal necrolysis (TEN) is a life-threatening disease characterized by extensive destruction of the epidermis [5]. To date, no cause other than drugs has been found in TEN although 5% of the cases remain "idiopathic" [22]. The mortality rate, which is higher than 40% in patients with more than 30% skin detachment is mainly due to septicemia and metabolic disturbances following the loss of epidermal integrity [11].

The mechanism leading to massive keratinocyte death in TEN is thought to be apoptosis [18]. Disregulations in the tumor necrosis factor-α (TNF-α) pathway, CD95 system (Fas ligand-CD95L, Fas receptor-CD95R) and calcium homeostasis in the epidermis are likely involved [18]. Indeed, TEN keratinocytes express large amounts of active CD95L able to induce apoptosis of CD95R-positive cells. CD95R, which belongs to the TNF/NGF receptor family is over-expressed in TEN epidermis.

The TEN initiation phase leading to keratinocyte apoptosis is followed by an amplification phase involving inflammatory cells [18]. An active role has been ascribed to T lymphocytes, particularly CD4+ cells in the dermis and CD8+ cells in the epidermis. In addition,

L1-protein-enriched macrophages and Factor XIIIa-positive dendrocytes appear also to play pathogenic roles in the epidermis and dermis, respectively.

In the past, systemic corticosteroids were used for targeting the inflammatory reaction in TEN [8]. However, there was no evidence for a benefit in the healing process, while they worsened the prognosis by increasing the risk of septicemia [8]. Only a few case reports have reported other treatment modalities including cyclophosphamide [6], pentoxyfilline [23], thalidomide [31] and cyclosporin A (CsA) [1, 9, 12, 15, 18, 21, 25, 26, 32]. Although T lymphocytes are the main target of CsA, the drug could also somewhat prevent keratinocyte apoptosis in TEN [15]. Some TEN patients have also been treated with intravenous human immunoglobulins (IVIg) [2, 10, 14, 19, 20, 24, 28–30]. The rationale for this treatment was to block CD95R on keratinocytes. The early promising clinical results of IVIg treatment in TEN were subsequently challenged [2]. Histological and immunohistological assessments of the IVIg effects in TEN skin have not been studied so far.

We presently report on the modifications in the inflammatory infiltrate (T lymphocytes, macrophages, type I dendrocytes) and in the epidermal CD95R expression during IVIg and CsA treatments. Both of these treatments were administered to two TEN patients. A comparison was made with supportive care given to two other TEN patients.

TEN was diagnosed in six patients admitted to the burn units of the University Hospital of Liège and the Brussels Military Hospital (Belgium). The diagnosis was established following previously defined criteria [4]. In each case, a recent drug intake was disclosed. The salient characteristics of the patients are listed in Table 2. The disease duration on admission was recorded since the first day of erythematous rash or mucous membrane involvement. Our center representing a secondary reference center, the disease duration on admission was sometimes quite long. On admission, the patients were placed on a fluidized bed and benefited from supportive and antiseptic care measures including daily baths. In two randomized patients, IVIg (Sandogobuline®, Novartis Pharma, Basel, Switzerland) was administered daily at a dose of 0.75 g/kg body weight for five consecutive days. These IVIg batches were not tested for their anti-Fas activity. In two other randomized patients, intravenous CsA (Neoral Sandimmun®, Novartis Pharma, Basel, Switzerland) was administered at a daily dosage of 5 mg/kg body weight for five consecutive days. We retrieved from our files skin biopsies from two other patients who had been hospitalized in the mid-nineties,

at a time when IVIg and CsA were not advocated in TEN. These patients had received supportive care only, without any drug currently considered active in TEN.

Punch biopsies were performed at admission (D1). They were taken from early bullous lesions (< 24 h), and from the apparently uninvolved skin at 2 cm outside a blister. They were formalin-fixed and paraffin-embedded. Five days later (D5), two other biopsies were obtained next to the first samples, that is, one from an apparently intact skin area and the other from a previously altered area.

Slides were stained with hematoxylin and eosin. In addition, the three-step avidin-biotin method was applied to a panel of antibodies (Table 1). Appropriate positive controls (graft versus host reaction, bullous pemphigoid, staphylococcal scalded skin syndrome) and negative controls (normal skin) were considered [16].

Computerized image analysis (Leica imaging systems, Qwin, Cambridge, UK) was used to assess the cell densities relative to each immunolabeling. Blinded evaluations were performed by an observer unaware of the clinical condition and treatment. Five contiguous representative fields ($\times 400$) located in the central part of the damaged epidermis were analyzed in each lesion. The cell densities were expressed as the number of positive cells per surface unit ($10,000\ \mu m^2$). The anti-CD95R antibody labeled keratinocytes as well as some inflammatory cells in the epidermis. Image analysis allowed to discriminate among these cell types by only recording the largest positive cells corresponding to the keratinocytes.

Re-epithelialization at D5 appeared to be moderately improved in IVIg and CsA-treated patients compared to the untreated patients (Table 2). No difference was suggested between CsA- and IVIg-treated patients. However, the small number of patients does not permit firm conclusion in terms of re-epithelialization. No difference in time before hospital discharge was evidenced between the IVIg- and CsA-treated patients, and the untreated patients (Table 2). One patient of each of the IVIg-and CsA-groups died from sepsis.

At D1, subepidermal blisters resulted from complete epidermal necrosis underlined by a discrete mononuclear cell infiltrate. The clinically uninvolved skin looked histologically normal. At D5, the aspect of bullous skin remained similar in three patients (pts 2, 4, 5). A regenerative epidermis was present in three other patients (pts 1, 3, 6) without any residual blister. In these latter patients, a discrete superficial perivascular lymphoid infiltrate underlined the thickened epidermis. In all six patients, the clinically unaltered skin at D5

Table 1 Panel of monoclonal (Mo) and polyclonal (Po) antibodies

Antibody	Source	Dilution	Specificity
Mo, UCLH1 anti-CD45R0	Dako	1:100	Mature T cells
Po, anti-factor XIIIa	BioGenex	1:300	Type I dendrocytes
Mo, anti-CD95 (Fas)	Dako	1:25	CD95 receptor
Mo, anti-CD68	Dako	1:50	Lysosomes in reactive macrophages

Table 2 Toxic epidermal necrolysis patients

Patients	Treatment	Age, sex	Duration of disease on admission (day)	Epidermal loss of body surface (%)	Medical history	TEN complication	Time to hospital discharge or death (day)	Re-epithelialization at day 5 (%)
1	IVIG	66, M	14	80	Achalasia	Gangrenous cholecystis	23	>75
2	IVIG	76, F	10	40	Kidney insufficiency	Sepsis (MRSA)	Death, 11	>50
3	CsA	56, F	6	30	Alcoolic cirrhosis	Sepsis (P. aeruginosa)	Death, 16	>50
4	CsA	32, F	3	65		Sepsis (Hemophilus influenza)	+22	>75
5	Supportive	50,M	6	30	Insulino-dependent Diabetes Psoriasis Polynevritis		+22	>50
6	Supportive	48, M	5	50	HIV		+20	>50

remained histologically normal or showed a discrete superficial perivascular lymphoid infiltrate.

Immunohistochemical results are presented in Tables 3 and 4. In bullous skin, Factor XIIIa + dendrocytes represented the most abundant cell population in the superficial dermis. Compared to the D1 pretreatment status, their number was reduced or remained similar at D5 in all patients but in patient 6 they were more numerous. At D1, few CD45R0 + T lymphocytes and rare CD68 + macrophages were disclosed in the epidermis and superficial dermis of all patients. These cell densities decreased or remained similar at D5. The most prominent difference between treated TEN patients and those under supportive care only was found in the CD95R + keratinocytes. Their number was greatly decreased at D5 in IVIg (-95.8% and -32.5%) and CsA-treated patients (-37.9% and -67.7%). In contrast, they markedly increased ($+450\%$ and $+92.5\%$) in the two patients under supported care (Fig. 1). In the clinically uninvolved skin, Factor XIIIa + dendrocytes, CD45R0 + lymphocytes and CD68 + macrophages were in a small number in all TEN patients, without any obvious change in their densities between D1 and D5. CD95R was expressed on many keratinocytes at D1 in most of the biopsy specimens. In contrast, this immunoreactivity was disclosed in less than 1% of the keratinocytes in other non-TEN diseases. At D5, the number of CD95R + keratinocytes moderately increased in IVIg-treated TEN patients, decreased in CsA-treated patients and greatly increased in TEN patients under supportive care only (Fig. 2). In some TEN patients, the number of CD95 + keratinocytes was greater in the clinically uninvolved skin than in the corresponding bullous lesions, both at D1 and D5. However, due to the small number of TEN patients, no firm relationship was found between the clinical course and the densities of CD95R + keratinocytes and inflammatory cells.

High IVIg dosages were recently used to treat some TEN patients [2, 10, 14, 19, 20, 24, 28–30]. The rationale for this treatment relied on the in vitro inhibition of FasR–FasL interaction and keratinocytes apoptosis by Ig. This effect is likely mediated by an anti-CD95R activity rather than by an interaction with CD95L. In vitro studies have also shown that high dose Ig inhibit CD95R-mediated apoptosis of keratinocyte in a dose-dependent relationship [27, 30]. However, the in vitro protective effect is observed at variable concentrations according to the different IVIg batches available for in vivo usage [20, 27]. This observation points to the difficulties in standardizing IVIg treatment of TEN. Preliminary clinical results about this treatment remain controversial so far, showing either improvement [10, 14, 19, 20, 24, 28–30] or worsening [2] in TEN morbidity and mortality. All the clinical non comparative studies reported so far were not supported by histological examination.

Cyclosporin A was also proposed for reversing TEN progression [1, 9, 12, 15, 21, 25, 26, 32]. The suppressive action of CsA primarily targets T-cell functions, and it inhibits the macrophage activation [15]. CsA also re-

Table 3 Immunohistochemistry in bullous skin of TEN patients on admission (D1) and at D5

| Patients	Epidermis								Dermis					
	CD95R D1	CD95R D5	FXIII D1	FXIII D5	CD68 D1	CD68 D5	CD45RO D1	CD45RO D5	FXIII D1	FXIII D5	CD68 D1	CD68 D5	CD45RO D1	CD45RO D5
1 (IVIG)	33.7	1.4	0	0	1.9	1	0.7	0	14.5	12.3	5.9	7.8	1.9	0.1
2 (IVIG)	42.8	28.9	0	0	1	0	12.2	0.7	14.1	4.7	1.2	0.8	13.2	3.2
3 (CsA)	15.3	9.5	0	0	0	0	13.7	1	5	1.2	2.6	0.4	11.6	1.5
4 (CsA)	12.7	4.1	0	0	2.1	1.7	6.3	0	2.4	2.5	2.1	1.7	5.2	1.7
5 (C)	2	9	0	0	0	0	0	1	12.7	2.1	2.3	0.6	0.5	0.6
6 (C)	10.7	20.6	0	0	4.7	1.4	5.4	0.7	5.9	12.8	6.2	7.4	14	1

C Control patient under supportive care only

Table 4 Immunohistochemistry in uninvolved skin of TEN patients on admission (D1) and at D5

Patients	Epidermis								Dermis					
	CD95 D1	CD95 D5	FXIII D1	FXIII D5	CD68 D1	CD68 D5	CD45RO D1	CD45RO D5	FXIII D1	FXIII D5	CD68 D1	CD68 D5	CD45RO D1	CD45RO D5
1 (IVIG)	5	9.4	0	0	0	0	0	0	2.7	6	0.1	5.5	0.9	0.1
2 (IVIG)	16.2	20.5	0	0	0	0	0	6.9	4.5	2.2	0.3	0.4	2.1	4.2
3 (CsA)	7.1	4.1	0	0	0	0	0	0	1.6	0.9	0.2	1.8	2.6	2.3
4 (CsA)	16.7	7.2	0	0	0	0	0	0	1	0.6	0	1.1	0	0.4
5 (C)	7	20.2	0	0	0	0	0	0	1.5	5.2	1	0.6	0.7	0.7
6 (C)	1	28.1	0	0	0	0	0	0	2.8	1.6	0.7	0.8	1.4	0.4

C Control patient under supportive care only

Fig. 1 Computerized image analysis of the expression of CD95R in necrotic TEN epidermis, before treatment (*D1*) and after a 5-day treatment with IVIG (*a1, a2*) or CsA (*b1, b2*) in comparison with a patient benefiting from supportive measures only (*c1, c2*). CD95+ keratinocytes appear in *blue*
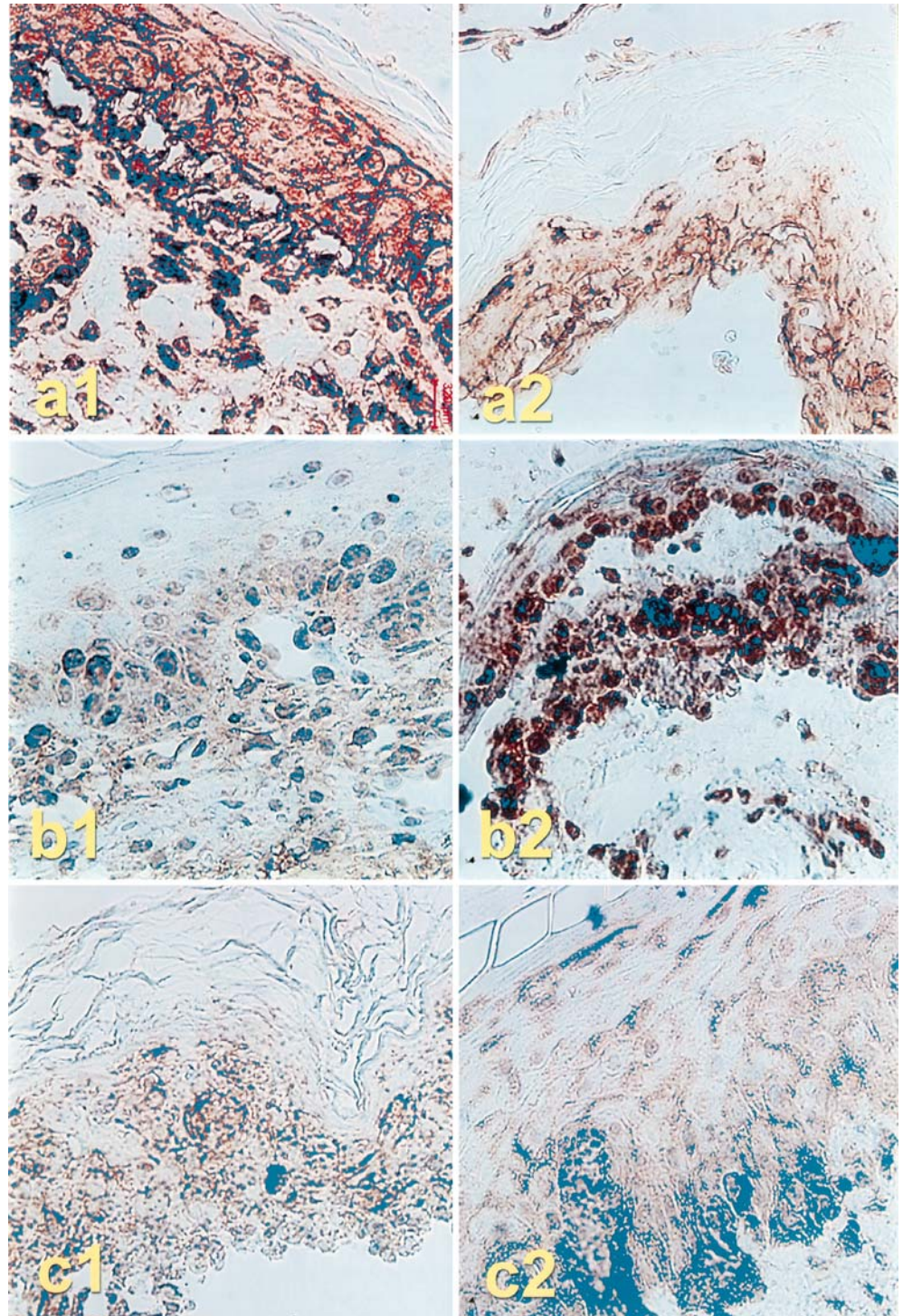

duces TNF-α secretion by human epidermal keratinocytes in vitro [15]. This cytokine is one of the major ones involved in TEN epidermal destruction. Treatment of mice with subcutaneously injected CsA was shown to inhibit TNF-α gene expression by about 70% in the skin [15]. In addition, the CsA immunosuppressive effect may partly be mediated by inhibition of the activation of the FasR–FasL system. In vitro, CsA inhibits the drug-induced expression of CD95R and CD95L-mRNA and blocks drug-mediated apoptosis of some cell types [7]. Only few TEN cases have been treated with CsA in uncontrolled studies [1, 9, 12, 21, 25, 26, 32]. Clinical beneficial effects were generally reported, but not supported by specific biological evaluations.

The apoptosis marker CD95R is shown here to be downregulated in clinically involved TEN skin at completion of a 5-day IVIg or CsA treatment. CD95R was moderately increased (IVIg) or decreased (CsA) in

Fig. 2 Computerized image analysis of the expression of CD95R in clinically uninvolved TEN epidermis, before treatment (*D1*) and after a 5-day treatment with IVIG (*d1, d2*) or CsA (*e1, e2*) in comparison with a patient benefiting from supportive measures only (*f1, f2*). CD95+ keratinocytes appear in *blue*
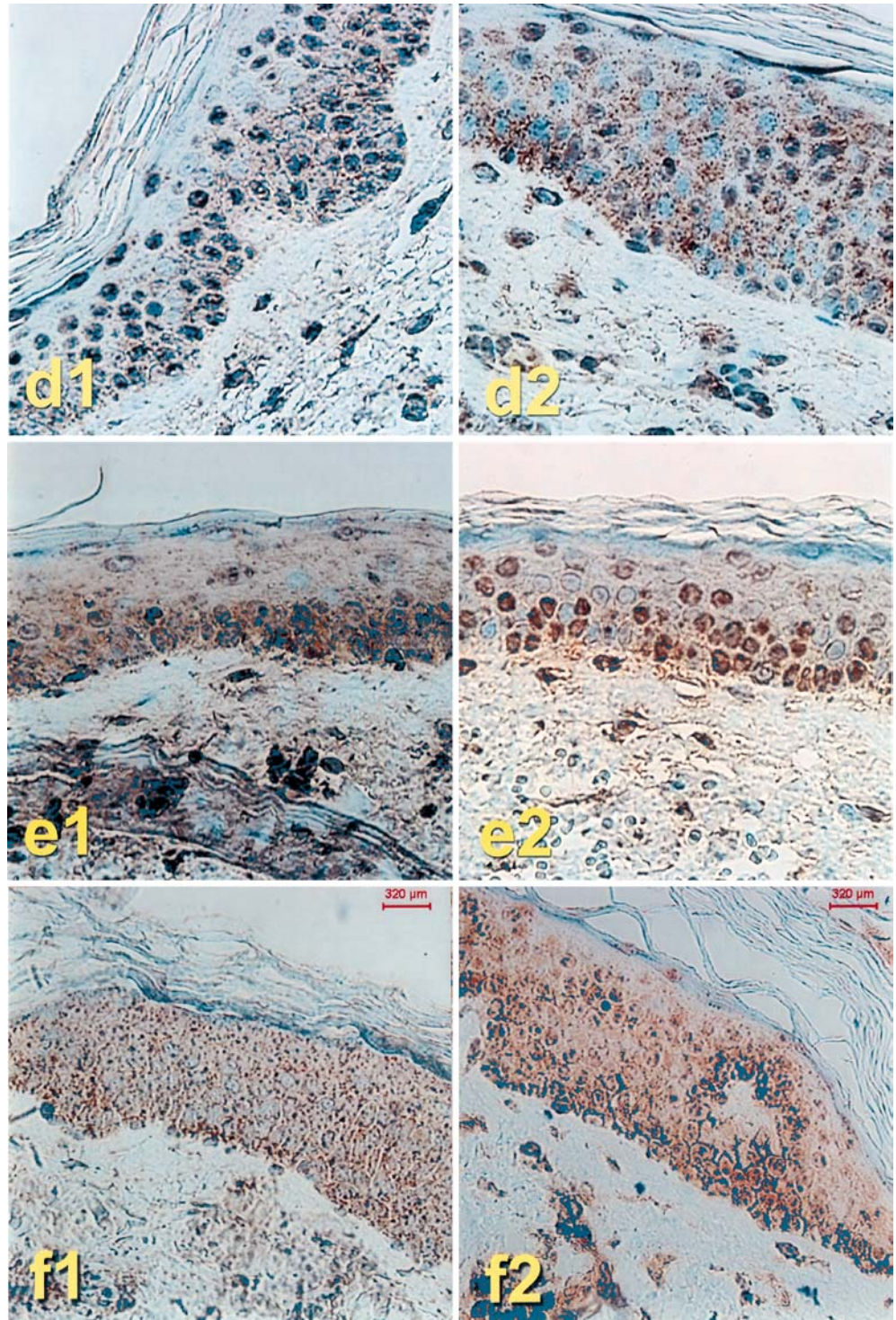
the clinically uninvolved skin of TEN patients. In contrast, in TEN patients under supportive care only, CD95R was markedly increased at D5 compared to D1 both in the uninvolved and involved skin. Hence, the present in vivo findings are in line with the in vitro inhibitory effects of IVIg and CsA on the CD95R-CD95L system. No effect of IVIg or CsA was evidenced on the densities of the TEN inflammatory cell infiltrate. This was surprising for CsA, which exhibits a potent inhibitory effect on activated T lymphocytes. However, the inability of CsA to downregulate some types of cutaneous cell inflammatory infiltrate was previously noticed, especially in alopecia areata [13].

Although both IVIg and CsA treatments inhibit the CD95R-CD95L system, this effect may not be powerful

enough to initiate a clinically relevant improvement in re-epithelialization. Similarly, these drugs appear to fail to control TEN morbidity and mortality at least when major risk factors are present. In our series, one IVIg-treated patient died from sepsis. She was the oldest of the patients and she suffered from previous kidney deficiency. These factors are two negative predictive factors for TEN outcome [3]. The administered 0.75 g/kg/day IVIg dosage was also lower than the newly recommended dosage (1 g/kg/day) [2, 20, 28]. Indeed, higher IVIg dosage might have impaired her renal function, leading to increased morbidity risk [2]. Sepsis was also the cause of death of one of the CsA-treated patients. This patient suffered from cirrhosis, which is a major mortality risk factor in TEN.

The densities of the inflammatory cell infiltrates were moderate in all TEN patients at D1. Only Factor XIIIa+ dendrocytes appeared boosted at that time. This supports the concept considering that the early phase of the TEN process is probably initiated by the keratinocytes themselves and the dermal dendrocytes [18]. The pathomechanisms leading to keratinocyte destruction are probably multiple and different at each stage of epidermal maturation [17]. The apoptosis pattern may involve the calcium-independent CD95 system in the deeper epidermal layers and a calcium-dependent system in the superficial epidermis. The present findings suggest that the destruction of keratinocytes is provoked by simultaneous activation of several apoptosis pathways. Blocking CD95R may prevent the apoptosis progression, but has little effect on the epidermal healing phase. Indeed, the rate of re-epithelialization induced by both IVIg and CsA during the early TEN phase did not appear different from patients under supportive care only as assessed by the clinical outcome and by microscopy at D5. A regenerating epidermis was demonstrated in one CsA and one IVIg-treated patient, but also in one patient under supportive care only.

In conclusion, both IVIg (0.75 g/kg/day) and CsA (5 mg/kg/day) treatments appear to inhibit the apoptotic CD95 pathway in TEN patients. This effect might not be effective enough to improve the early clinical evolution and prognosis in TEN patients with high-risk factors.

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