

Rapid resolution of toxic epidermal necrolysis with anti-TNF- α treatment

To the Editor:

Toxic epidermal necrolysis (TEN) is a rare, life-threatening, adverse drug reaction characterized by widespread apoptosis and detachment of the epidermis. It is associated with a high mortality rate of about 30%. Various drugs have been reported to induce TEN (eg, antibiotics, anti-convulsants, and nonsteroidal anti-inflammatory drugs). The optimal treatment modality is still highly debated. On the basis of recent reports, the beneficial effect of intravenous immunoglobulin¹ has been challenged.²

The cytokine TNF- α exerts potent proinflammatory effects in protective immune responses against a variety of infectious agents. On a cellular level, TNF- α might result in cell death caused by direct cytotoxicity and induction of apoptosis. Neutralization of TNF- α has been shown to be effective in noninfectious inflammatory disorders, such as Crohn's disease, rheumatoid arthritis, and psoriasis.³ In patients with TEN, TNF- α is strongly expressed in keratinocytes and macrophages⁴ of lesional skin, and high concentrations are found in cutaneous blister fluid.⁵ Thus far, just one patient with cotrimoxazol-induced TEN has been reported to benefit from anti-TNF- α treatment.⁶ With this background, we initiated a therapy with anti-TNF- α antibodies (infliximab) in a 69-year-old woman who was admitted to our clinic with skin detachment rapidly evolving within the previous 24 hours. Before admission, the patient had been treated with various drugs. During the last 2 years, she was occasionally taking diclofenac for headache, with the last time being 2 days before admission. Acitretin therapy for the last 1½ years for pustular psoriasis was stopped 3 weeks before admission. In addition, she had been taking thyroxine for 1 year and propranolol for 3 months for hypothyroidism and arterial hypertension, respectively. The clinical picture with widespread detachment of the epidermis (>30% body surface area) and positive Nikolski sign (Fig 1), as well as the histologic findings with apoptotic keratinocytes (data not shown), were typical for TEN. Lymphocyte proliferation assay results were positive for diclofenac (maximum stimulatory index of 2.1) but negative for thyroxine, propranolol, and acitretin (maximum stimulatory indices of 1.6, 0.8, and 1.2, respectively). Control lymphocyte

proliferation assay results with diclofenac were negative in nonsensitized individuals. These results, together with the fact that acitretin was readministered 2 months later without recurrence of TEN, indicates that diclofenac most probably was the culprit drug. Patients with TEN have been shown to have increased serum levels of soluble Fas ligand (sFasL).¹ We therefore determined this marker to confirm our diagnosis of TEN. By using multiplex beads coated with anti-FasL antibody (R&D Systems Inc, Minneapolis, Minn), the serum levels of sFasL were determined. Until day 9 after infliximab infusion, serum samples from our patient showed increased levels of sFasL (maximum, 73 pg/mL); on day 15 the serum level of sFasL was less than the detection limit (<8 pg/mL). In a control experiment with serum from a patient with generalized pustular psoriasis, the serum levels of sFasL were less than the detection limit.

On admission, all medications were stopped. Three days after the initial symptoms and after exclusion of an infectious disease, the patient received one single infusion of 5 mg/kg body weight of infliximab (Remicade; Essex Chemie, Luzern, Switzerland). Epidermal detachment stopped within 24 hours, and after 5 days, re-epithelialization was almost complete (Fig 1). This is clearly faster than the reported clinical response time of 2.1 ± 0.8 days after intravenous immunoglobulin therapy.⁷

To further assess the role of TNF- α in tissue destruction of TEN, we examined TNF- α expression in the skin in the course of anti-TNF- α therapy. Early lesions (ie, red skin areas without clinical signs of detachment) were analyzed with monoclonal mouse anti-human TNF- α antibody (Alexis Corp, San Diego, Calif). Tissue sections before anti-TNF- α therapy showed strong immunoreactivity for TNF- α in the keratinocytes of the outer necrobiotic parts of the epidermis and also in scattered basal and suprabasal keratinocytes (Fig 2). Furthermore, TNF- α was also strongly expressed in perivascular inflammatory cells in the dermis and in inflammatory cells infiltrating the epidermis. Twenty-four hours after anti-TNF- α therapy, immunoreactivity for TNF- α was markedly decreased in lesional skin, reaching even lower levels than in normal skin samples. In correlation with protein immunoreactivity, *TNFA* mRNA expression dramatically decreased after anti-TNF- α therapy, decreasing to less than the *TNFA* mRNA levels in normal human skin (Fig 2, D). To this

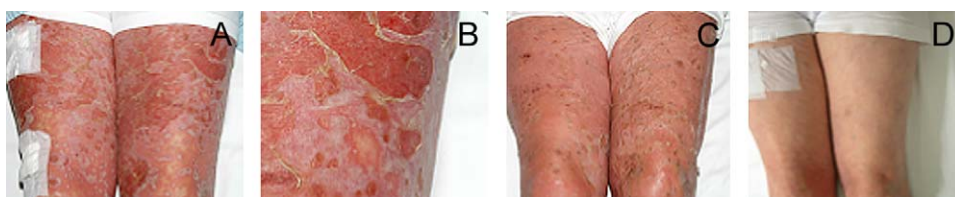


FIG 1. A, Erythema and widespread detachment of the epidermis before therapy. B, Details of the epidermal detachment. C, Two days after intravenous anti-TNF- α therapy, skin detachment has completely stopped, and erythema is fading. D, Six days after therapy, there is almost complete re-epithelialization.

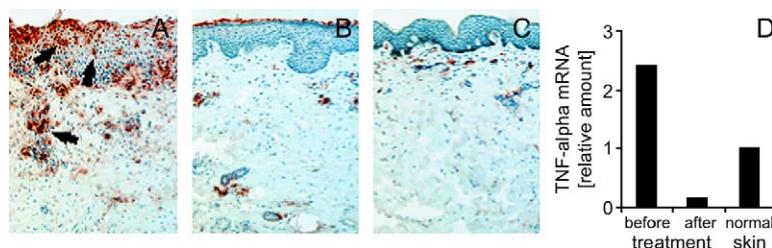


FIG 2. TNF- α expression *in situ*. Cryostat sections of patient's lesional skin before (**A**) and 24 hours after (**B**) treatment with anti-TNF antibody (infliximab) and of a healthy control subject (**C**) were stained with monoclonal mouse anti-human TNF- α antibody. Arrows in Fig 2, A, indicate high TNF- α expression in the epidermis and dermis. **D**, *TNFA* mRNA expression was quantified before and after TNF- α treatment and as a control in normal skin.

end, total RNA was extracted from skin biopsy specimens with Trizol reagent (Invitrogen, Carlsbad, Calif). *TNFA* mRNA was quantified by using a TNF- α TaqMan gene expression assay on a 7300 Real Time PCR System (Applied Biosystems, Foster City, Calif), according to the manufacturer's indications. This reduction of TNF- α expression on the mRNA and protein level was paralleled by a dramatic recovery from erythema and a complete stop of epidermal detachment. It is highly interesting that neutralization of the cytokine TNF also downregulates its mRNA production. TNF- α is first produced as a transmembrane protein with an intracellular tail. Membrane-bound TNF- α is secreted by cleavage of the extracellular part by metalloproteinases. Infliximab has been shown to bind to soluble and membrane-bound TNF- α and in addition to induce apoptosis of TNF- α -producing cells, especially of activated T cells.⁸

The rapid resolution of skin lesions in TEN after systemic anti-TNF- α therapy with infliximab opens new perspectives for the treatment of this rare but life-threatening condition and strongly supports the hypothesis that TNF- α produced by keratinocytes, as well as monocytes/macrophages, is significantly involved in the tissue damage.

We thank A. Urwyler and M. Schedlowski, Institut für Verhaltenswissenschaften, ETH Zürich, Switzerland, for determining the serum concentration of sFasL, and W. Pichler, Institut für Allergologie und Klinische Immunologie, for performing the lymphoproliferation assays. We also thank Essex Chemie AG for providing financial support for the PCR and immunohistochemical analysis.

Robert E. Hunger, MD, PhD

Thomas Hunziker, MD

Urs Buettiker, MD

Lasse R. Braathen, MD, PhD, MHA

Nikhil Yawalkar, MD

Department of Dermatology

University of Bern

Inselspital

3010 Bern

Switzerland

REFERENCES

- Viard I, Wehrli P, Bullani R, Schneider P, Holler N, Salomon D, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science* 1998;282:490-3.

- Wolff K, Tappeiner G. Treatment of toxic epidermal necrolysis: the uncertainty persists but the fog is dispersing. *Arch Dermatol* 2003;139:85-6.
- Lebwohl M. Psoriasis. *Lancet* 2003;361:1197-204.
- Paquet P, Nikkels A, Arrese JE, Vanderkelen A, Pierard GE. Macrophages and tumor necrosis factor alpha in toxic epidermal necrolysis. *Arch Dermatol* 1994;130:605-8.
- Nassif A, Moslehi H, Le Gouvello S, Bagot M, Lyonnet L, Michel L, et al. Evaluation of the potential role of cytokines in toxic epidermal necrolysis. *J Invest Dermatol* 2004;123:850-5.
- Fischer M, Fiedler E, Marsch WC, Wohlrab J. Antitumor necrosis factor- α antibodies (infliximab) in the treatment of a patient with toxic epidermal necrolysis. *Br J Dermatol* 2002;146:707-9.
- Prins C, Vittorio C, Padilla RS, Hunziker T, Itin P, Forster J, et al. Effect of high-dose intravenous immunoglobulin therapy in Stevens-Johnson syndrome: a retrospective, multicenter study. *Dermatology* 2003;207:96-9.
- Van den Brande JM, Braat H, van den Brink GR, Versteeg HH, Bauer CA, Hoedemaeker I, et al. Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. *Gastroenterology* 2003;124:1774-85.

Available online August 18, 2005.
doi:10.1016/j.jaci.2005.06.029

Nebulizer output for methacholine challenges with the KoKo Digidoser

To the Editor:

Unrecognized variation in nebulizer output can affect the results of bronchoprovocation tests¹ because the apparent provocation concentration of bronchoconstrictor causing a 20% decrease in FEV₁ (PC₂₀) might be different from the true value. Accordingly, the American Thoracic Society (ATS) guidelines for methacholine challenge tests recommends that the output of a nebulizer be determined before it is placed into service and periodically thereafter.² For the 5-breath dosimeter method, the guideline recommends that the nebulizer be calibrated to deliver 9 μ L per 0.6-second actuation (equivalent to 0.900 $\pm$ 0.09 mL/min). We attempted to follow this guideline for the KoKo Digidoser (model no. 323200; Ferraris Respiratory, Louisville, Colo) and found that the nebulizer output was low and could not be calibrated to meet this requirement.

The KoKo Digidoser is a commonly used dosimeter in the United States for methacholine challenges. It is an all-in-one system combining spirometer and dosimeter in one handheld unit connected by a cable to a computer containing the challenge software (Fig 1, upper panel).