
Etanercept therapy for toxic epidermal necrolysis

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Background: Toxic epidermal necrolysis (TEN) is a severe and potentially lethal drug reaction for which no standard treatment is available.

Objective: To describe a case series of patients with TEN treated with a single dose of etanercept.

Methods: We observed 10 consecutive patients with TEN. For each patient, we recorded the presence of comorbidities and all the drugs recently started (ie, in the last month). In all cases, 50 mg of etanercept was administered in a single subcutaneous injection. The clinical severity of disease was computed using the SCORe of Toxic Epidermal Necrosis (SCORTEN) scale. Using the probabilities of death linked to each level of SCORTEN score, we calculated the expected probability of death in our patients. Healing was defined as complete reepithelialization, and a time to healing curve was then obtained using the Kaplan–Meier method.

Results: All patients promptly responded to treatment, reaching complete reepithelialization without complications or side effects. The median time to healing was 8.5 days.

Limitations: This is a small, uncontrolled case series.

Conclusion: These preliminary results suggest the possibility that tumor necrosis factor–alpha may be an effective target for control of TEN, a dangerous skin condition for which no effective cure has yet been found. (*J Am Acad Dermatol* 2014;71:278-83.)

Key words: adverse drug reaction; etanercept; therapy; toxic epidermal necrolysis.

Toxic epidermal necrolysis (TEN), also known as Lyell syndrome, is a severe adverse drug reaction that is characterized by extensive skin necrosis and detachment of the epidermis and mucous membranes.¹ TEN is considered a medical emergency; its estimated incidence is 0.4 to 1.2 cases per million persons per year, and mortality rates range from 25% to 35%.²⁻⁴ Early symptoms can be nonspecific (eg, fever, stinging eyes, and dysphagia) and are followed by a widespread erythematous rash and livid macules that have a tendency to coalesce rapidly. In the next phase, symptoms include flaccid bullae, epidermal detachment over large

areas (>30% of the body surface area [BSA]), and painful hemorrhagic erosions of the mucous membranes in >90% of patients.⁵ TEN is an idiosyncratic drug reaction: allopurinol, antibiotics, anticonvulsants, and nonsteroidal antiinflammatory drugs seem to be the most common triggers.⁶ No treatment—including systemic steroids,⁷ which have been the standard therapy for TEN for about 20 years—has yet been shown to be effective in controlled clinical trials. Recently, encouraging but sporadic results of treatment with tumor necrosis factor–alpha (TNF- α) antagonists have been described in the international literature.⁸⁻¹⁸

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The aim of this study was to evaluate the efficacy and safety of etanercept in a series of TEN patients.

METHODS

We observed 10 consecutive patients who were hospitalized with TEN at the IDI-IRCCS dermatologic institute in Rome, Italy, between 2011 and 2012. We obtained written informed consent from all patients for treatment with etanercept. The compassionate use of etanercept for TEN had been approved by the Ethical Committee of the IDI-IRCCS.

On admission, when a diagnosis of TEN was hypothesized, information on all probable causative medications was collected, and such treatments were immediately stopped.

All patients underwent the following examinations:

routine blood tests, immunologic tests (ie, antinuclear antibodies, anti-extractable nuclear antigen antibodies, antiskin antibodies [ASA-IIF], antidesmogleins 1 and 3, anti-BPs 180 and 230, serology for hepatitis C and B viruses, and HIV infection, Quantiferon test), chest radiographs, electrocardiography, and cardiologic evaluation.

For each patient, we recorded the presence of comorbidities and all of the drugs recently started (ie, in the last month).

TEN was diagnosed clinically according to the following criteria: denudation of the epidermis in sheets during the acute phase, with blisters and erosions covering >30% of the BSA, often with a positive Nikolsky sign.⁴ Moreover, other common clinical features of TEN have been evaluated, such as painful inflammation and ulceration of the mucosal surfaces and ocular and genital involvement. When the clinical features were not clear-cut characteristics of TEN, the suspected diagnosis was confirmed histologically.

All patients were given intravenous fluid replacement, aseptic handling, and nutritional support. However, given the great diversity of the problems posed by each case, no standard approach was adopted; rather, supportive therapy was tailored to the needs of each patient. In all cases, 50 mg of etanercept was administered in a single subcutaneous injection. All patients were treated as soon as possible, and invariably within 6 hours from hospitalization. The time from symptom onset is not known precisely, but patients

were usually referred to our center within 72 hours of symptom onset.

The clinical severity of disease was computed using the SCORE of Toxic Epidermal Necrosis (SCORTEN) scale.¹⁹ The scale ranges from 0 to 7 and attributes 1 point for the presence of each of the following 7 items: age >40 years; heart rate >120 beats per minute; the presence of malignancies; BSA involvement >10%; serum urea >10 mmol/L; serum bicarbonate <20 mmol/L; and serum glucose >14 mmol/L.

Using the probabilities of death linked to each level of SCORTEN score, published in the original validation study, we calculated the expected probability of death in our patients.

Healing was defined as complete reepithelialization (ie, the complete absence of erosions), and time to heal-

ing was recorded for each patient. A time to healing curve was then obtained using the Kaplan–Meier product-limit estimates method.²⁰

RESULTS

The single components of the SCORTEN for each patient are shown in [Table I](#). Three patients were in the higher category of SCORTEN severity (ie, a score ≥ 5), while no patient was in the lower category (ie, a score of 0-1).

Other important characteristics of the patients (ie, sex, age, comorbidities, culprit drugs, and time to healing) are summarized in [Table II](#).

Nine patients presented with comorbidities, which were considered severe in 8 cases. Three patients had malignancies: 2 had a primary cerebral neoplasm and 1 had a brain metastasis from breast cancer. The drug most frequently involved in triggering TEN was carbamazepine, which is used to prevent epileptic seizures.

All patients promptly responded to treatment, reaching complete reepithelialization without complications or side effects ([Fig 1](#)). The exact binomial 95% confidence interval for the observed proportion of deaths (ie, 0) ranges from 0% to 30.8%, which does not contain the expected probability of death in our sample, computed on the basis of patients' SCORTEN scores (46.9%).

Time to healing ranged from 7 to 20 days (median, 8.5 days). The Kaplan–Meier curve for all observations is shown in [Fig 2](#).

CAPSULE SUMMARY

- Toxic epidermal necrolysis is a severe, potentially lethal drug reaction for which no effective cure has yet been found.
- Ten patients with toxic epidermal necrolysis treated with a single dose of etanercept (50 mg) showed complete healing without complications or side effects.
- Tumor necrosis factor– α may be an effective new therapeutic approach for toxic epidermal necrolysis.

Table I. Detail of the SCORTEN components and SCORTEN scores in 10 patients with toxic epidermal necrolysis treated with etanercept

SCORTEN components	Patient no.									
	1	2	3	4	5	6	7	8	9	10
Age >40 y	1	1	0	1	1	1	1	1	1	1
Heart rate >120 beats/min	1	0	1	1	1	1	0	0	0	0
Cancer or hematologic malignancy	1	0	0	0	0	1	0	1	0	0
>10% body surface area involvement	1	1	1	1	1	1	1	1	1	1
Serum urea level >10 mmol/L	1	1	0	0	0	0	0	1	0	0
Serum bicarbonate level <20 mmol/L	1	0	0	0	0	0	0	1	0	0
Serum glucose level >14 mmol/L	0	0	0	0	1	1	0	1	0	1
SCORTEN score	6	3	2	3	4	5	2	6	2	3

SCORTEN, SCORe of Toxic Epidermal Necrosis.

DISCUSSION

In our series of TEN patients treated with a single dose of etanercept, healing was obtained in all cases without severe side effects.

Findings reporting increased levels of TNF- α in skin biopsy specimens²¹ or in blister fluid and serum²² of TEN patients encouraged the adoption of biologic therapy with anti-TNF- α monoclonal antibodies (infliximab) or with a soluble fusion protein binding to human TNF- α (etanercept). Although reports of TEN managed with biologic agents are scarce, the present study confirms the reported effectiveness of anti-TNA- α drugs.⁸⁻¹⁸

Only 2 patients with TEN treated with 2 doses of etanercept (25 mg/day on days 4 and 8¹⁶ and at an interval of 1 day,¹⁷ respectively) have been described. In the first patient,¹⁶ who had previously been treated with corticosteroids without benefit, epidermal detachment ceased within 24 hours of the first dose. Unfortunately, he then died of disseminated intravascular coagulation 10 days after admission. The other patient¹⁷ was given corticosteroids both previously and simultaneously with etanercept, and epidermal detachment stopped 2 days after the first etanercept injection. A patient with acute generalized exanthematous pustulosis/TEN overlap syndrome¹⁸ was successfully treated with etanercept 25 mg (twice in a week), with disease arrest being achieved within 48 hours of the first injection.

Although these case reports describe promising outcomes, none were controlled studies, and the overall patient number is still small. Nonetheless, such outcomes are much more favorable than those obtained with “standard” approaches.²³⁻³⁹

Table II. Patients with toxic epidermal necrolysis treated with etanercept: Sex, age, comorbidities, culprit drugs, and time to healing

	Patient no.									
	1	2	3	4	5	6	7	8	9	10
Gender	F	M	F	F	M	M	F	F	M	F
Age, y	57	70	28	62	73	78	72	50	71	55
Culprit drug	Carbamazepine	Ofloxacin	Lansoprazole, azathioprine	Methylprednisolone	Ciprofloxacin	Carbamazepine	Phytotherapy product	Carbamazepine	Carbamazepine	Diclofenac
Time to healing (days)	12	8	8	12	8	7	8	20	9	9
Comorbidities	Cerebral neoplasm	Bronchopneumonia	Systemic lupus erythematosus	Pemphigus vulgaris	Bronchopneumonia	Cerebral neoplasm	—	Cerebral metastases (breast cancer)	Intracranial hemorrhage (head trauma)	Periarthritis

F, Female; M, male.



Fig 1. Two patients with toxic epidermal necrolysis before (**A** and **C**) and after treatment with a 50 mg single-dose subcutaneous injection of etanercept (**B** and **D**), respectively.

The pathogenesis of TEN is unclear. The observations that TEN recurrence is faster and more severe if the patient is reexposed to the culprit drug⁴⁰; that drug-specific T cells are found in the skin of TEN patients⁴¹; and that patients with certain human leukocyte antigen haplotypes are at a greater risk of developing TEN when exposed to certain drugs^{42,43} strongly support a role for T cell-mediated immune responses in its pathogenesis. However, the immune cell infiltration (including cytotoxic T cells) found in the skin of TEN patients seems insufficient to induce massive keratinocyte apoptosis, suggesting that some cytotoxic proteins and/or cytokines may amplify the process. The upregulation of FasL expression on the surface of keratinocytes from TEN patients has been shown to induce keratinocyte apoptosis by engaging constitutively expressed Fas.⁴⁴ A recent study⁴⁵ has advanced the hypothesis of a link between the drug-specific immune response and the induction of target cell death by apoptotic molecules (including FasL) by positing a role for inducible nitric oxide synthase

(iNOS). iNOS is significantly increased in the epidermis of TEN patients,⁴⁶ and in keratinocytes it is regulated by interferon-gamma and TNF- α , whose levels in blister fluid from TEN patients are increased.^{47,48} According to the aforementioned construct, an iNOS/nitric oxide/FasL pathway might link the immune activation and the widespread keratinocyte apoptosis seen in TEN: the authors⁴⁵ noted that activated T cells secrete large amounts of TNF- α and interferon-gamma, which have the ability to induce iNOS expression and nitric oxide production by keratinocytes, resulting in FasL upregulation and Fas-mediated keratinocyte apoptosis. Etanercept therapy would act by blocking this inflammatory pathway via TNF- α inhibition.

It is also noteworthy that etanercept, in addition to TNF- α , also blocks lymphotoxin α (LFT- α), which has been recently reported to play an important role in the pathogenesis of graft-versus-host disease,⁴⁹ which shares clinical,⁵⁰ histologic, and pathogenetic^{51,52} resemblances to TEN. We therefore believe that LFT- α could play a role in TEN pathogenesis,

Time-to-healing in 10 patients with toxic epidermal necrolysis treated with etanercept

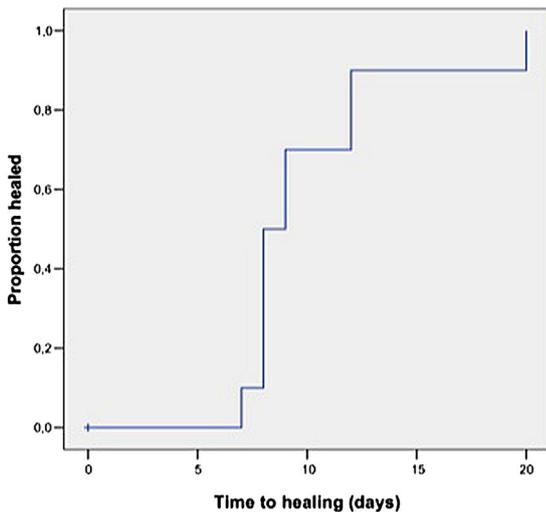


Fig 2. Kaplan-Meier curve for time to healing (days) in 10 patients with toxic epidermal necrolysis treated with Etanercept.

and its block, together with that of TNF- α , may be at least partially linked to the robust and rapid therapeutic effect of etanercept seen in our patients.

The present study is small and lacks a control group. However, to the best of our knowledge, this is the largest series of TEN patients to have been treated with a biologic agent. Moreover, despite the small sample size, the upper 95% confidence interval for the 0 observed deaths (30.8%) is well below the expected probability of death computed in our sample on the basis of patients' SCORTEN scores (46.9%). In addition, given the high expected probability of death among patients undergoing the "standard" treatments, it may actually be unethical to assign patients to a control group.

The present study is also characterized by a number of advantages, because it was not only carried out at a single institution, but also in a single clinical unit; this entails that all patients were seen by the same dermatologists, observed in the same environmental conditions, and treated in a standardized manner consisting of a single dose of etanercept, while all other TEN medications were withdrawn.

We hope that these results may encourage other clinicians to test this therapeutic approach, which may provide a breakthrough for a dangerous skin condition for which no effective cure has yet been found.

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