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Case Series

Dermatology Section

Single Dose of Etanercept Injection: A Game Changer in Toxic Epidermal Necrolysis: A Case Series

RAJKUMAR KANNAN[1], SAMUEL JEYARAJ DANIEL[2], PARIMALAM KUMAR[3], LAVANYA KAVIMANI[4]

ABSTRACT

Toxic Epidermal Necrolysis (TEN) is a rare hypersensitivity reaction to drugs, characterised by widespread erythema, full-thickness epidermal necrosis with mucosal involvement, and extensive apoptosis. It is a dermatological emergency and can be lethal if not promptly treated. The use of steroids in managing TEN is controversial since no gold standard therapy exists. However, a single dose of subcutaneous injection of Etanercept (a Tumour Necrosis Factor-alpha (TNF-α) inhibitor) at a dosage of 50 mg has shown promise in preventing mortality and reducing hospital stay. The authors present a case series of six TEN patients, out of which three received a single dose of Etanercept injection. All patients who received Etanercept showed a positive response, achieving complete re-epithelialisation with a median healing time of nine days. In conclusion, injection of Etanercept, a TNF-α inhibitor, effectively inhibits Fas-Fas ligand activation, thus preventing apoptosis and extensive necrosis.

Keywords: Adverse drug reaction, Apoptosis, Re-epithelialisation, Tumor necrosis factor-α inhibitors

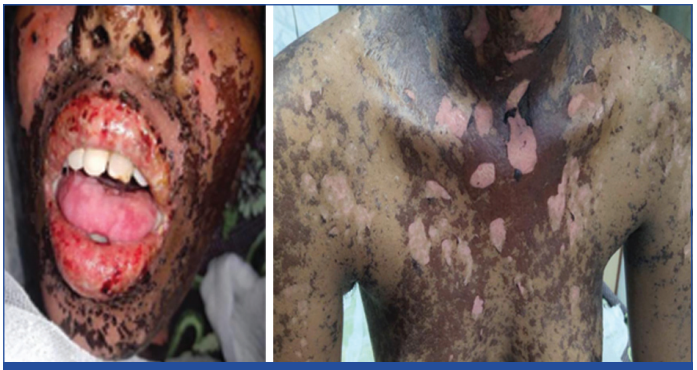
INTRODUCTION

Toxic Epidermal Necrolysis (TEN) is a rare hypersensitivity reaction to drugs, considered a dermatological emergency. It is clinically characterised by widespread erythema, full-thickness epidermal necrosis with mucosal involvement, and extensive apoptosis. The pathogenesis of TEN remains unclear. However, several observations support a role for T-cell mediated immune responses in its development: faster and more severe recurrence of TEN upon re-exposure to the same offending drug, presence of drug-specific T-cells in the skin of TEN patients, and increased risk of developing TEN in individuals with specific Human Leukocyte Antigen (HLA) haplotypes when exposed to certain drugs [1,2]. Etanercept, a TNF-α inhibitor, has a shorter half-life compared to infliximab and adalimumab. In this case series, the authors describe six TEN patients, of whom three received a single dose of Etanercept injection.

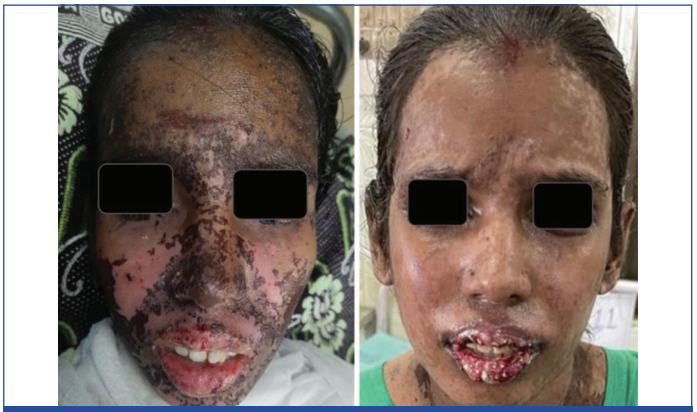
CASE SERIES

Case 1

A 27-year-old female with no co-morbidities presented at the Department of Dermatology with a 2-day history of fever and diffuse painful erythematous rashes all over her body. Thirteen days prior to the symptoms, the patient had taken Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) over the counter for joint pain. At the time of presentation, the patient was afebrile but tachycardic, with a pulse rate of 120/min and a blood pressure of 110/70 mm Hg. Physical examination revealed multiple areas of tender, poorly demarcated erythematous to dusky macules, blisters, and extensive skin detachment involving 70% of the Body Surface Area [Table/Fig-1]. The oral cavity showed painful erosions and crusting [Table/Fig-1]. The Pseudo Nikolsky sign was positive. A Tzanck smear was performed, which showed necrotic basal cells. Laboratory studies were within normal limits. As TEN is a clinical diagnosis, the SCORTEN value was calculated and found to be three. The patient was started on intramuscular injection of Dexamethasone 2 cc and continued on a maintenance dose of oral steroids, gradually tapering by 5 mg every week. On the second day of admission, the patient developed steroid-induced hyperglycaemia. After adequate titration with insulin and obtaining consent, a single subcutaneous dose of injection Etanercept 50 mg was administered. The patient responded well to the treatment, achieving complete re-epithelialisation on day 8 [Table/Fig-2]. There were no major complications or side effects post-injection. The patient is currently under follow-up.



[Table/Fig-1]: Case 1 showing erythema and peeling of skin over face, trunk before treatment; Desquamation of mucosal upper lip and lower lip with erosions.

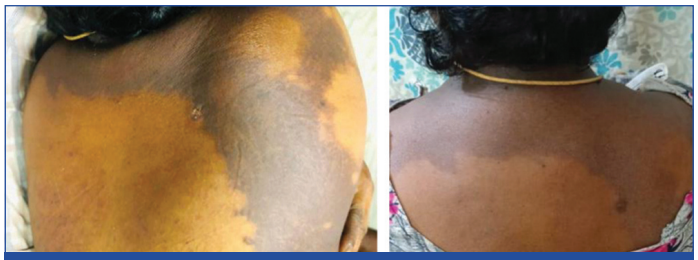


[Table/Fig-2]: Case 1 showing erythema and peeling of skin over face before treatment (left) and resolution of lesions after treatment (right).

Case 2

A 45-year-old female, a known case of systemic hypertension, presented with multiple hypopigmented patches, and after appropriate investigations (positive Slit skin smear with confirmatory histopathological findings), she was diagnosed with Hansen's disease. She was initiated on Multi Bacillary Multi Drug Therapy (MB-MDT). On the second day of treatment with MB-MDT, the

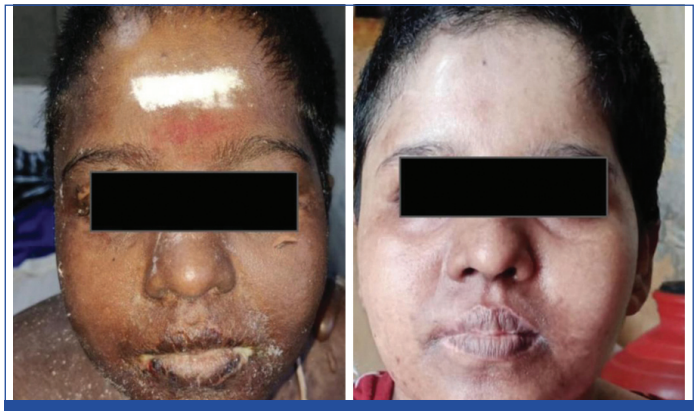
patient developed a painful rash that started on her upper back and spread to cover her entire trunk. Dermatological examination revealed tenderness, an erythematous to dusky macular eruption with multiple erosions and skin peeling, exhibiting a bizarre shape with a positive pseudo -Nikolsky sign on the upper back [Table/Fig-3]. The detachment affected 40% of the Body Surface Area (BSA). Laboratory investigations were within normal limits, except for a white cell count of 21,000/cm^3 and elevated Liver Function Test (LFT) levels. The diagnosis of Toxic Epidermal Necrolysis (TEN) was made, with a SCORTEN value of three. On the third day of admission, the patient received a single subcutaneous dose of injection Etanercept 50 mg, and she responded well to the treatment. She is currently under regular follow-up.



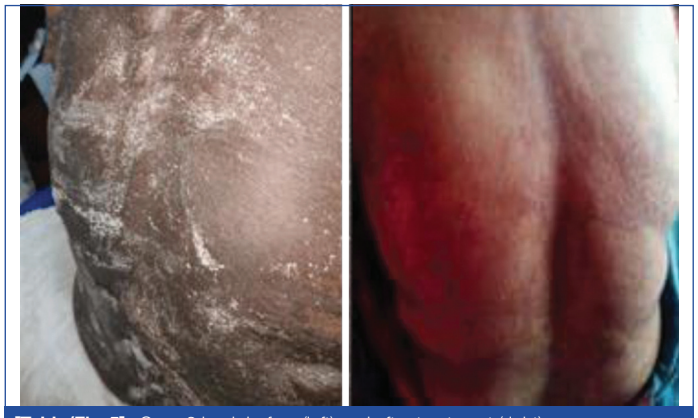
[Table/Fig-3]: Case 2 back before (left) and after treatment (right).

Case 3

A 30-year-old female, known to have epilepsy, switched her medication from levetiracetam to phenytoin. She subsequently developed erythema, a rash, and skin peeling affecting 90% of the Body Surface Area (BSA) [Table/Fig-4]. Laboratory investigations revealed elevated levels of C-Reactive Protein (CRP) (110), LDH (1056), and liver enzymes (SGOT 1067, SGPT 789). The SCORTEN value was 2. On the third day of admission, the patient received a single subcutaneous dose of injection Etanercept 50 mg. After seven days, the patient recovered, and on follow-up [Table/Fig-5].



[Table/Fig-4]: Case 3 face before (left) and after treatment (right).



[Table/Fig-5]: Case 3 back before (left) and after treatment (right).

Case 4

A 68-year-old male was brought to the casualty department in an unresponsive state, exhibiting severe peeling of the skin involving the entire body with mucosal involvement. The patient had fever two days prior and received an injection of ceftriaxone at a nearby hospital. Eight hours after receiving the injection, the patient developed erythema and skin peeling, starting on the face and progressing to involve more than 70% of the Body Surface Area (BSA). The diagnosis was severe cutaneous adverse drug reaction to ceftriaxone [Table/Fig-6]. The SCORTEN value was 3. The patient was initiated on intramuscular injection of Dexamethasone 8 mg. Unfortunately, the patient went into cardiac arrest due to sepsis before receiving injection Etanercept.

[Table/Fig-6]: Case 4 before treatment: face (left) and back (right).

Case 5

An 11-year-old female child developed Toxic Epidermal Necrolysis (TEN) with involvement of more than 90% of the Body Surface Area (BSA) on the third day of starting Phenytoin, which was given for febrile seizures [Table/Fig-7]. The SCORTEN value was 3. The patient was treated with a single injection of Dexamethasone 8 mg as the only available treatment option. Unfortunately, Injection Etanercept could not be given due to its non-availability. On the twelfth day, the child succumbed to cardiac arrest.

[Table/Fig-7]: Case 5 showing redness and peeling of skin over face (left) and back (right).

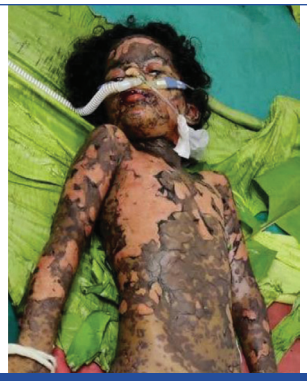
Case 6

A seven-year-old female child developed Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) in response to Cefixime/Gentamicin, which were administered for fever and abdominal pain at a local hospital. Four hours after receiving the injection, the child developed erythema and skin peeling, involving 100% of the Body Surface Area (BSA) [Table/Fig-8]. The SCORTEN value was four. The patient was treated with intramuscular injection of Dexamethasone 8 mg, along with intravenous Immunoglobulin (IVIG) calculated at 2 g/kg. Unfortunately, despite the treatment, the child could not be revived.

In summary, injection Etanercept was found to be a life-saving drug, reducing the time for re-epithelialisation to less than a week and resulting in a shorter hospital stay [Table/Fig-9-11].

DISCUSSION

In this case series of six patients with Toxic Epidermal Necrolysis (TEN), three patients were treated with a single dose of injection Etanercept



[Table/Fig-8]: Case 6 before treatment.

haplotypes when exposed to certain drugs indicate a role for T-cell mediated immune responses in its pathogenesis [5,6].

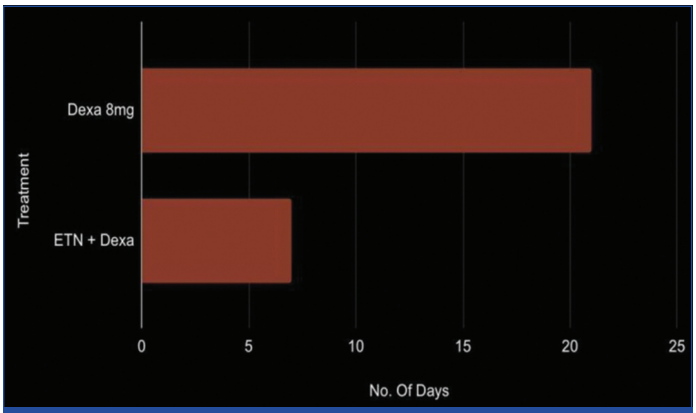
The immune cell infiltration, including cytotoxic T-cells, found in the skin of TEN patients seems insufficient to induce massive keratinocyte apoptosis, suggesting that some cytotoxic proteins and/or cytokines may amplify the process. Upregulation of FasL expression on the surface of keratinocytes from TEN patients has been shown to induce keratinocyte apoptosis through engagement with constitutively expressed Fas [6,7]. According to the proposed mechanism, an inducible Nitric Oxide Synthase (iNOS)/nitric oxide/FasL pathway may link immune activation and widespread keratinocyte apoptosis in TEN. Activated T-cells secrete TNF-alpha and interferon-gamma, which can induce iNOS expression and nitric oxide production by keratinocytes,

Pt. No.	Age/Sex	Body surface area %	Offending drug	SCORTEN	Mortality %	Etanercept	Other Rx	Status
1	27/F	50	NSAIDS/Paracetamol	3	35	Given on D2	Dexa 8 mg	Recovered after 8 days
2	45/F	40	Dapsone	3	35	Given on D2	Dexa 8 mg	Recovered after 12 days
3	30/F	90	Phenytoin	2	12	Given on D3	Dexa 8 mg	Recovered after 7 days
4	68/M	70	Ceftriaxone	3	35	Not given	Dexa 8 mg	Expired
5	11/F	90	Phenytoin	3	35	Not given	Dexa 8 mg	Expired
6	7/F	100	Cefixime	4	58	Not given	IVIG	Expired

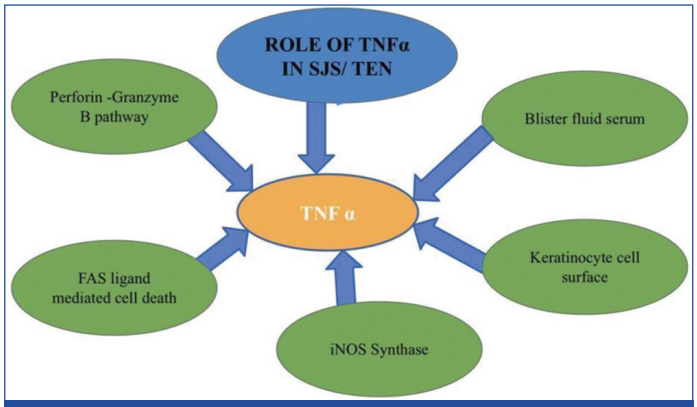
[Table/Fig-9]: Summary of case series.
NSAIDs: Non steroidal anti-inflammatory drugs; Dexa: Dexamethasone; IVIG: Intravenous Immunoglobulin

Case no.	Age/Sex	Total WBC count (/µL)	Hb %	Sr. Urea (mmol)	Sr. Creatinine (mg/dL)	RBS	SGOT (U/L)	SGPT (U/L)	LDH (U/L)	CRP (mg/dL)	ESR (mm/hr)
1	27/F	7900	11.6	17	0.7	247	45	34	178	7	22
2	45/F	21600↑	9.4	25	0.7	230	77↑	168↑	212↑	4	46↑
3	30/F	12000	10	19	0.7	102	1067↑	789↑	1056↑	110↑	45↑
4	68/M	18000	12	26	0.8	456	51	46	121	34↑	32↑
5	11/F	11500	11	55↑	1.2	212	67	56	234↑	156↑	22
6	7/F	23000↑	10	64↑	0.8	323	123↑	21	212↑	89↑	34↑

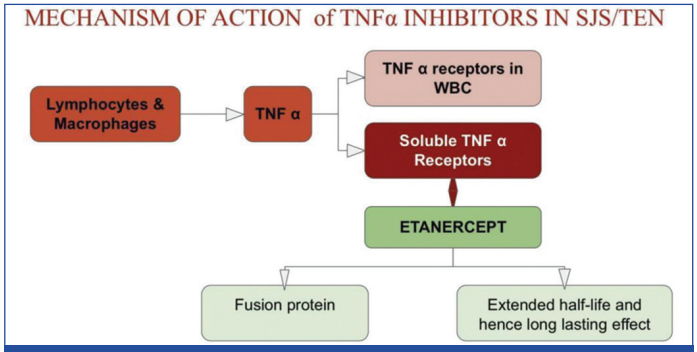
[Table/Fig-10]: Summary of investigations of cases.
WBC: White blood cells; Hb: Haemoglobin; Sr: Serum; RBS: Random blood sugar; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase; LDH: Lactate dehydrogenase; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate



[Table/Fig-11]: Time for re-epithelialisation in dexamethasone alone versus Etanercept with Dexamethasone.



[Table/Fig-12]: Role of TNF α in SJS/TEN.



[Table/Fig-13]: Mechanism of action of TNF α inhibitors in SJS/TEN.

50 mg. These patients showed healing and faster re-epithelialisation without severe side effects [Table/Fig-12,13]. Previous findings reporting increased levels of TNF-alpha in skin biopsy specimens [1] or in blister fluid and serum [2] of TEN patients have supported the use of biologic therapy with anti-TNF-alpha monoclonal antibodies (infliximab) or soluble fusion proteins binding to human TNF-alpha (etanercept). The present case series further confirms the reported effectiveness of anti-TNF-alpha drugs [1,3-4].

It is important to note that these case reports do not constitute randomised controlled studies, and the overall number of patients is still small. Nonetheless, the outcomes are more favourable compared to "standard" approaches. The pathogenesis of TEN is still not fully understood. However, observations such as faster and more severe recurrence of TEN upon re-exposure to the same offending drug, the presence of drug-specific T-cells in the skin of TEN patients, and the increased risk of developing TEN in patients with certain HLA

leading to FasL upregulation and Fas-mediated keratinocyte apoptosis. Etanercept therapy acts by blocking this inflammatory pathway through TNF-alpha inhibition.

It is worth noting that in addition to TNF-alpha, etanercept also blocks lymphotoxin alpha (LFT-alpha), which has been reported to play a role in the pathogenesis of graft-versus-host disease, a condition that shares clinical, histologic, and pathogenetic similarities with TEN. This suggests that TNF-alpha could play a role in TEN pathogenesis, and its blockage, along with that of LFT-alpha, may contribute to the robust and rapid therapeutic effect of etanercept observed in the patients of this study. Paradisi A et al., published a case series of 10 cases of TEN treated with a single dose of etanercept, reporting that all patients responded to treatment with complete re-epithelialisation achieved without side effects, with a median time to heal of 8.5 days [8]. Wang CW et al., concluded that TNF-alpha inhibitors are effective for the treatment of Cytotoxic T lymphocyte (CTL)-mediated Severe Cutaneous Adverse Reactions (SCARs) [9].

CONCLUSION(S)

As TNF-alpha has been demonstrated within the blister fluid, serum, and on the keratinocyte cell surface, and TNF-alpha upregulates iNOS in keratinocytes, consequently leading to FasL-mediated cell death through the perforin-granzyme B pathway as the final terminal event, the authors found that the duration of hospital stay was reduced, and steroid-related complications were eliminated with the use of injection Etanercept. Morbidity and mortality related to adverse drug reactions were greatly reduced, and the treatment outcomes were impressive. Etanercept is a wonderful tool in the dermatologist's armamentarium to minimise deaths and promote faster re-epithelialisation with minimal side-effects.

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PARTICULARS OF CONTRIBUTORS:
1. Professor, Department of Dermatology, Venereology and Leprosy (DVL), MMC & RGGH, Chennai, Tamil Nadu, India.
2. Associate Professor, Department of Dermatology, Venereology and Leprosy (DVL), MMC & RGGH, Chennai, Tamil Nadu, India.
3. Professor, Department of Dermatology, Venereology and Leprosy (DVL), MMC & RGGH, Chennai, Tamil Nadu, India.
4. Senior Resident, Department of Dermatology, Venereology and Leprosy (DVL), MMC & RGGGH, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Lavanya Kavimani,
Senior Resident, Department of Dermatology, Venereology and Leprosy (DVL),
Rajiv Gandhi Hospital, Parktown, Chennai-03, Tamil Nadu, India.
E-mail: lavanyakavimani94@gmail.com

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