

Etanercept treatment of Stevens-Johnson syndrome and toxic epidermal necrolysis



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ABSTRACT

Background: Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a severe cutaneous adverse reaction to drugs with considerable morbidity and mortality. Immunomodulators for SJS/TEN including systemic corticosteroids and intravenous immunoglobulin (IVIG) have been widely used in clinical practice. Emerging evidence suggested the therapeutic effects of tumor necrosis factor- α antagonists on SJS/TEN.

Objective: To compare the efficacy and safety of IVIG and systemic steroids in conjunction with or without etanercept, a tumor necrosis factor- α inhibitor, for patients with SJS/TEN.

Methods: We undertook a retrospective review of 41 patients with SJS/TEN admitted to our institution from 2015 to February 2021. A total of 25 patients with integrated data were involved in this study, of which 14 patients were treated with IVIG and corticosteroids and 11 were in addition given etanercept. The clinical characteristics, duration of hospitalization, exposure time to high-dose steroids, and the total amount of systemic steroids were analyzed.

Results: In comparison to conventional therapy, conjunction with etanercept reduced the duration of hospitalization (13.5 vs 19.0 days; $P = .01$), the exposure time of high-dose steroids (7.1 vs 14.9 days; $P = .01$), and the overall amount of systemic steroid (925 mg vs 1412.5 mg; $P = .03$) in patients with SJS/TEN. No pronounced adverse effects were observed within 6 months of follow-up after the treatment.

Conclusion: The add-in of etanercept at the time of initiating conventional therapy could be a superior option to accelerate disease recovery and reduce the high dose and total amount of systemic steroids without pronounced adverse events in patients with SJS/TEN.

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Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are regarded as a disease spectrum of severe cutaneous adverse reactions that are both most often caused by medications and less frequently by infections.¹ These 2 disorders are classified according

to the body surface area (BSA) of epidermal detachment: SJS (BSA < 10%), overlap SJS-TEN (BSA 10%–30%), and TEN (BSA > 30%). The estimated incidence of SJS/TEN is 2 to 7 per million patients per year, and the mortality rate ranges from 5% to 50%.^{1–3} Causative drugs for SJS/TEN are categorized into groups, such as anticonvulsants, antibiotics, allopurinol, and nonsteroidal anti-inflammatory drugs (NSAIDs). Carbamazepine and allopurinol are the most relevant medicines in Asian countries.⁴ Both SJS and TEN are delayed hypersensitivity reactions, characterized by erythema, exanthema, blisters, and bleeding erosions, particularly in the eye and oral and genital areas.^{5,6} In general, at least 2 sites of mucous membranes are involved in SJS/TEN. The severity-of-illness score for toxic epidermal necrolysis (SCORTEN), with scale of 0 to 7, is generally applied to evaluate disease severity and predict mortality of patients with SJS/TEN.⁷

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The pathogenesis of SJS/TEN remains to be elucidated. Keratinocyte necrosis and epidermal damages are the classic histopathologic changes of SJS/TEN which are thought to be induced by cytotoxic T lymphocyte-mediated inflammatory reactions.^{3,8} Researchers have revealed that culprit drugs or their metabolites presented by human leukocyte antigen molecules on antigen-presenting cells could initiate T cell activation and promote the intensive immune responses found in SJS/TEN.^{2,3,5,9,10} Several cytotoxic mediators secreted by T cells and natural killer cells, such as granulysin, perforin, and granzyme, have been found to mediate extensive keratinocyte apoptosis in SJS/TEN.^{3,5} Recent studies have reported that tumor necrosis factor- α (TNF- α) was markedly increased in blisters and patient serum and might induce Fas-mediated keratinocyte apoptosis in TEN.^{11–15}

Primary treatment for SJS/TEN consists of prompt cessation of the causative agent and initiation of supportive therapy.¹⁶ Many studies have described the efficacy of immunomodulators for SJS/TEN treatment. Of them, systemic corticosteroids and intravenous immunoglobulin (IVIG) have been widely used in clinical practice.⁸ However, the clinical outcomes of these therapies remain controversial and the disease management calls for better improvement.^{17,18} In the last decade, several case reports suggested the therapeutic effects of TNF- α antagonists on SJS/TEN.^{19–25} A randomized control study was conducted to assess the efficacy and safety of etanercept (TNF- α blocker) as a monotherapy for SJS/TEN compared with corticosteroids alone. The results indicated that etanercept could accelerate the skin healing process with reduction of TNF- α and granulysin in blisters.¹⁰ Still, the optimal treatment for SJS/TEN remains controversial. Actually, the promising results of TNF- α blockers as a monotherapy raise an important question of whether TNF- α blockers could evidently improve the prognosis when combined with conventional medicine.

We herein compared the outcomes of patients with SJS/TEN who received etanercept as an additional therapy to those treated with conventional regimens only. This study adds to the knowledge of treatment of SJS/TEN.

Methods

The procedures and protocols of this study were reviewed and approved by the Clinical Research Ethics Board of Sun Yat-sen Memorial Hospital (protocol approval number SYSEC-KY-KS-2021-092). We identified 41 patients discharged from the Department of Dermatology, Sun Yat-sen Memorial Hospital, with a confirmed diagnosis of SJS/TEN from January 2015 to February 2021. All patients were diagnosed with having SJS/TEN based on the medical history and the typical clinical presentations (mucosal involvement, target lesions, and skin detachment). According to the percentage of body surface area (BSA) of epidermal detachment, patients were classified into the following 3 groups: SJS (BSA < 10%), overlap SJS-TEN (BSA 10%–30%), and TEN (BSA > 30%).⁸ The diagnosis was further confirmed by the negative results of indirect immunofluorescence in testing autoantibodies to desmoglein (Dsg) 1, Dsg3, BP230, and BP180 that excluded the autoimmune bullous diseases. Patients with the following conditions were excluded from this study: seropositive for human immunodeficiency virus, hepatitis B virus infection, active tuberculosis or any other active severe infections, lymphoma, heart failure, and pregnancy. Patients were carefully informed about the risks and benefits of etanercept therapy. Data were reviewed and confirmed by 3 doctors.

Demographic data, clinical features, culprit drugs, treatments, and prognosis were obtained from electronic medical records. The culprit drug was determined when algorithm of drug causality for epidermal necrolysis score was more than or equal to 4; otherwise, it was recorded as “undefined.”²⁶ The clinical severity of SJS/TEN was evaluated using SCORTEN based on vital signs and laboratory findings within 24 hours after admission. Patients discharged when they reached 100% skin healing and more than 50% oral mucosa healing.

Medications administered during hospitalization (corticosteroids, IVIG, etanercept) and patient outcomes, including length of hospitalization, were recorded. Serum levels of TNF- α were measured in the clinical laboratory at Sun Yat-sen Memorial Hospital using tumor necrosis factor- α assay kit (chemiluminescent assay, Siemens LKNF1, Siemens, Llanberis, United Kingdom) through IMMULITE 1000 system (Siemens Healthcare Diagnostics Inc, Camberley, United Kingdom) according to the manufacturers' instructions. Profound adverse events potentially associated with etanercept^{27,28} were defined as serious infections including sepsis and fascial infection, respiratory failure, hepatic abnormalities (liver enzymes 3 times higher than the normal range), hepatitis virus and tuberculosis infection, serious cardiovascular disease, occurrence of new malignant tumor and progression of original malignant tumor, and hematological damage (platelet count < 50,000/mm³, neutrophil count < 500 mm³) within 6 months after etanercept treatment.

All the analyses were performed using SPSS version 25.0 (IBM, Armonk, New York). Data were presented as mean and SD if in a normal distribution. Otherwise, they were presented with median and range. Statistical significance was determined using the Student's 2-tailed *t* test or Mann-Whitney *U* tests for quantitative variables whereas qualitative variables were compared using the χ^2 tests. *P* values less than .05 were considered significant.

Results

We identified 41 patients with a confirmed diagnosis of SJS/TEN from January 2015 to February 2021 (Fig 1). The youngest patient was 11 years old and the oldest one was 77 years old. After chart review, 8 patients were excluded for lack of IVIG treatment and 6 (1 in etanercept group vs 5 in steroids plus IVIG group) were excluded for lung infection and multiple organ dysfunction syndrome. One patient in the conventional group was excluded owing to insufficient data of steroid dose and 1 patient in the etanercept group was not included because the treatment was discontinued. Finally, 25 patients with integrated data were included in this study. Of them, 14 were treated with corticosteroids and IVIG and 11 in addition received at least 1 dose of etanercept. The average dose of IVIG was 0.4 g/kg/d for 3 to 5 days. The initial dosage of methylprednisolone was equivalent to 1 to 2 mg/kg/d prednisolone in both groups. Only 1 patient in the conventional group received methylprednisolone pulse therapy at the dosage of 250 mg/d for 5 days. If the recovery were undesirable, methylprednisolone dose was increased by an additional 50% above the initial dose for patients not responding to the initial therapy. Patients in combined therapy group received 25 mg of etanercept (or 50 mg for patients who weighed more than 65 kg).¹⁰ A second dose of etanercept was prescribed if skin lesions were not improved within 2 days after the initial dose. Early improvement was defined as “the absence of new mucocutaneous lesions, less exudate production of erosions, and negative Nikolsky's sign.”

The age, sex, skin detachment, mucosal involvement, disease severity measured by SCORTEN score, predicted mortality, and proportion of patients treated before admission to our institution were comparable between patients treated with and without etanercept (Table 1). Fever (63.6% vs 57.1%, respectively) and liver injury (63.6% vs 50.0%, respectively) were the most common extracutaneous manifestations in both cohorts. The distribution of causative drugs was illustrated in Table 2. NSAIDs accounted for the highest proportion of culprit drugs (20%), followed by carbamazepine (16%) and antibiotics (12%). NSAIDs (28.6%) and carbamazepine (36.4%) ranked the first causative drugs in patients who received conventional and etanercept therapy, respectively. Notably, camrelizumab, a programmed cell death protein 1 inhibitor for an antitumor treatment, was also one of the culprit drugs inducing TEN.

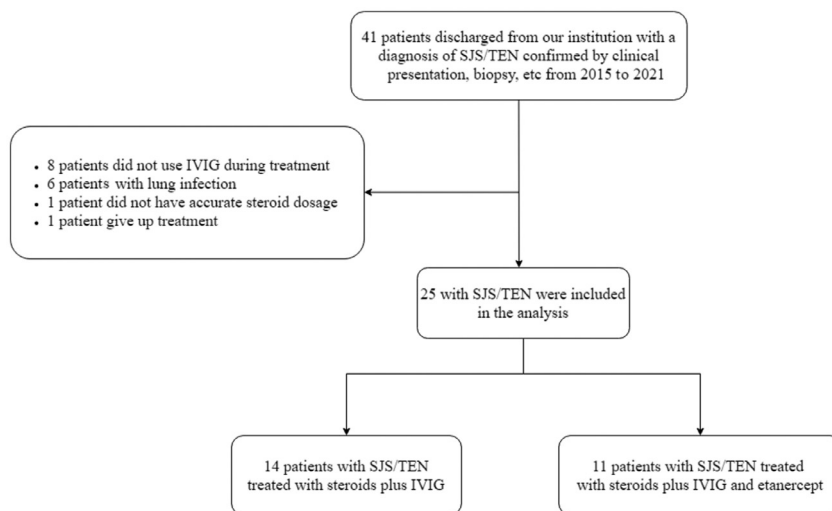


Figure 1. Flow diagram illustrating patient evaluation and assignment for inclusion in this retrospective study of conventional group (steroids plus IVIG) vs etanercept group (steroids plus IVIG and etanercept) for SJS/TEN. IVIG, intravenous immunoglobulin; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Comparisons of treatment medicine and the outcomes of the 2 groups were presented in Table 3. The length of hospitalization (median, 13.5 vs 19.0 days; $P = .01$) was significantly shortened in patients with etanercept therapy compared with those with conventional treatment. Furthermore, the exposure time of high-dose steroid (prednisone ≥ 1 mg/kg/d) and the cumulative dose of prednisone during hospitalization was markedly reduced in etanercept-treated patients compared with the conventional group (7.1 vs 14.9 days; $P = .01$; 925 vs 1412.5 mg; $P = .03$; respectively). Although no statistical significance, the dosage of prednisolone standardized by body weight in etanercept-treated group was nearly as half as much of the conventional group (14.6 vs 28.6 mg/kg; $P = .29$). No significant difference was noted between the 2 groups regarding the cumulative dose of IVIG (110.5 vs 125.0 g; $P = .51$). SCORTEN-predicted mortality rates were 12.2% in both groups. The details of 11 patients treated with etanercept are summarized in Table 4, and their representative photos before and after treatment are illustrated in Figure 2A and 2B. Most of the patients were treated with etanercept

within 24 hours after admission. There were 7 patients who received a single dose of etanercept, whereas 4 patients received the second dose owing to the remaining exudative erosions. All patients responded to the treatment with rapid re-epithelialization (≤ 3 weeks) but with no pronounced complications during hospitalization. No adverse reactions were observed after 6 months of follow-up. Of note, patient 6 developed skin lesions 8 days after the initial treatment with camrelizumab, a programmed cell death protein 1 inhibitor prescribed for her lung cancer. She received 1 dose of etanercept, responded very well, and was discharged 9 days after hospitalization even though her SCORTEN score was 3.

Serum levels of TNF- α were measured in 6 patients at different time points after the initial injection of etanercept. Of interest, serum TNF- α levels were temporarily elevated after first etanercept injection and then decreased gradually in 4 patients (eTable 1 and eFig 1).

Discussion

Although the benefits of systemic corticosteroids, IVIG, cyclosporine, and plasmapheresis have been reported in SJS/TEN treatment, evidences for systemic treatment are still insufficient. UK guidelines for the management of SJS/TEN, published in 2016, conclude that withdrawal of the culprit drug and multidisciplinary supportive care is prioritized over systemic treatment because of lack of evidence to reveal the benefits of the latter.⁸ However, Indian guidelines for SJS/TEN recommended early initiation of systemic corticosteroid therapy as the first-line treatment.²⁹ High or pulse doses of systemic steroid are most often used for SJS/TEN treatment in China. However, this therapy is associated with substantial adverse effects, including

Table 1
Baseline Characteristics of Patients in Etanercept Therapy and Conventional Therapy

Baseline characteristics	Etanercept (n = 11)	Conventional (n = 14)	P value
Age, y, M $\pm$ SD ^a	44.8 $\pm$ 21.6	40.4 $\pm$ 18.4	.58
Sex, n (%)			>.99
Male	6 (54.5)	8 (57.1)	
Female	5 (45.5)	6 (42.8)	
Fever ($>37.3^{\circ}\text{C}$), n (%)	7 (63.6)	8 (57.1)	>.99
Liver injury	7 (63.6)	7 (50.0)	>.99
Sepsis	3 (27.3)	2 (14.3)	.62
Skin detachment, n (%)			.18
BSA $\geq 10\%$	9 (81.8)	14 (100)	
BSA $< 10\%$	2 (18.2)	0	
Number of sites with mucosa erosion, n (%)			.14
1	2 (18.2)	8 (57.1)	
2	4 (36.4)	5 (35.7)	
3	3 (27.3)	1 (7.1)	
SCORTEN, M (R) ^b	2 (1-4)	2 (1-4)	.68
Predicted mortality, %, M (R) ^b	12.2 (3.9-62.2)	12.2 (3.9-62.2)	.68
Previous treatment (%)			.65
Yes	7 (63.6)	11 (78.6)	
No	4 (36.4)	3 (21.4)	

Abbreviations: BSA, body surface area; SCORTEN, severity-of-illness score for toxic epidermal necrolysis.

^aM $\pm$ SD represents mean $\pm$ standard deviation.

^bM (R) represents median (range). Number of sites with mucosa erosion represents the number of patients with varying degrees of mucosal damage.

Table 2
The Causative Drugs in Patients in Etanercept Treatment Group and Conventional Treatment Group

Causative drugs (%)	Etanercept (n = 11)	Conventional (n = 14)	Total (n = 25)
Antibiotics	0 (0.0)	3 (21.4)	3 (12.0)
NSAIDs	1 (9.1)	4 (28.6)	5 (20.0)
Carbamazepine	4 (36.4)	0 (0.0)	4 (16.0)
Allopurinol	1 (9.1)	1 (7.1)	2 (8.0)
Chinese medicine	1 (9.1)	1 (7.1)	2 (8.0)
Antitumor drugs	1 (9.1)	1 (7.1)	2 (8.0)
Others	0 (0.0)	2 (14.3)	2 (8.0)
Undetermined	3 (27.3)	2 (14.3)	5 (20.0)

Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

Table 3
Outcomes of Patients Treated With Etanercept Therapy and Conventional Therapy

Outcomes	Etanercept (n = 11)	Conventional (n = 14)	P value
Length of hospitalization, d, M $\pm$ SD ^a	13.5 $\pm$ 4.7	19.0 $\pm$ 5.7	.01 ^b
Prednisone $\geq$ 1mg/kg, d, M $\pm$ SD ^a	7.1 $\pm$ 4.3	14.9 $\pm$ 9.1	.01 ^b
Accumulated dose of prednisone, mg, M (R) ^c	925 (637.5–2125)	1412.5 (680–5275)	.03 ^b
Dose of prednisone, mg/kg, M (R) ^c	14.6 (9.8–34.5)	28.6 (12.4–75.4)	.29
Accumulated dose of IVIG, g, M $\pm$ SD ^a	110.5 $\pm$ 45.9	125.0 $\pm$ 59.5	.51

Abbreviation: IVIG, intravenous immunoglobulin.

^aM $\pm$ SD represents mean $\pm$ standard deviation.^bP < .05^cM (R) represents median (range).**Table 4**
Characteristics and Clinical Manifestations of 11 Patients Treated With Etanercept

Patient	Sex	Age (y)	Underlying diseases	Culprit drug	SCORTEN score	Etanercept dose	Hospital duration (d)
Patient 1	M	11	ITP	Undefined	1	25 mg on the first day	12
Patient 2	F	25	No	NSAIDs	2	25 mg on the first day	21
Patient 3	M	62	COPD	Undefined	2	25 mg on the first day	18
Patient 4	F	56	No	Carbamazepine	2	25 mg on the first day	15
Patient 5	M	71	Diabetes	Undefined	4	25 mg on the first and third days	11
Patient 6	F	35	Lung cancer	PD-1 inhibitor	3	25 mg on the first day	9
Patient 7	M	51	Schizophrenia	Carbamazepine	2	25 mg on the first day	7
Patient 8	M	23	Neural headache	Carbamazepine	2	25 mg on the second and fourth days	12
Patient 9	M	25	No	Chinese medicine	1	25 mg on the first and third days	12
Patient 10	F	71	Hypertension, diabetes	Allopurinol	4	25 mg on the first and third days	10
Patient 11	F	63	Hypertension, Sjogren syndrome	Carbamazepine	2	50 mg on the first day	21

Abbreviations: COPD, chronic obstructive pulmonary disease; F, female; ITP, immune thrombocytopenic purpura; M, male; NSAID, nonsteroidal anti-inflammatory drug; PD-1, programmed cell death protein 1; SCORTEN, severity-of-illness score for toxic epidermal necrolysis.

worsening of hypertension, infections, electrolyte imbalance, gastrointestinal hemorrhage, and behavioral effects.

Previous case studies have reported the therapeutic efficacy of etanercept for SJS/TEN.^{19,20,22,24} A randomized control study including 71 patients revealed that monotherapy with etanercept for SJS/TEN was superior to corticosteroids in skin healing aspect.¹⁰ Additional studies with a larger sample size are required to comprehensively evaluate the efficacy and safety of that therapy. Alternatively, etanercept could be adjunctive with conventional therapy in clinical practice. It was suggested that combination of etanercept with IVIG could be considered as an effective treatment for SJS/TEN.³⁰ A recent study revealed that adding TNF- α inhibitors to steroid treatment was superior to steroid monotherapy for SJS/TEN.³¹ Still, it remains unclear whether the combination of etanercept, steroids, and IVIG is effective for the treatment of SJS/TEN. Our data revealed fewer days of hospitalization in patients treated with additional etanercept therapy than those with conventional therapy. The results revealed that the combination of etanercept with corticosteroids and IVIG was associated with faster skin healing and reduced period of treatment in SJS/TEN. Of note, we

observed less exposure time to high-dose corticosteroids and lower cumulative dose of corticosteroids in the etanercept-treated group, compared with the conventional group. Accordingly, we suggested that etanercept combined therapy reduced the incidence of steroid-associated adverse effects and may hold the possibility as a steroid-sparing agent.

The mortality rate is another important consideration in patients with SJS/TEN. In our study, the predicted mortality was calculated according to the SCORTEN (Table 1). For the 14 patients treated with conventional therapy, the expected mortality of 11.2% (N = 1.568) was similar to the mortality of 11.2% for the 11 patients treated with etanercept. In our study, we did not observe any patient deaths, which may be largely owing to the exclusion of patients with lung infection and multiple organ dysfunction syndrome. A recent study suggested that a dramatic decrease of mortality over time was associated with the progressive improvement of supportive care in patients with SJS/TEN.³² Supportive care provided to our patients included a separate ward, fluid replacement, nutritional supplements, maintenance of an ambient body temperature, alginate dressing for denuded skin, and potassium permanganate baths.

**Figure 2.** Representative photos of 2 patients with SJS/TEN before and after treatment with etanercept in conjunction with IVIG and systemic steroids. IVIG, intravenous immunoglobulin; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

In the clinical trial of TNF- α antagonist as monotherapy for SJS/TEN treatment, 6 of 48 patients were reported with serious adverse events including sepsis and respiratory failure.¹⁰ In the present study, no severe adverse events were observed in patients treated with etanercept combined therapy. We postulated that the discrepancy might be owing to the baseline conditions of enrolled patients, or partially, attributable to more rapid disease control using etanercept plus IVIG and steroid. Given the limit of retrospective study, we were only able to identify the length of hospitalization, which made it difficult to compare our data with previous reports of etanercept alone where the outcome was the time of skin healing.^{10,19,22} Further research is warranted to compare clinical benefits between patients treated with etanercept monotherapy and etanercept as adjunctive therapy to identify better treatment protocols for SJS/TEN.²⁸

As found in Table 3, an 11-year-old patient was successfully treated with etanercept, and no adverse reactions were observed. SJS/TEN is not often found in children but is potentially serious and may be fatal.³³ Similar to adult patients, corticosteroids are most frequently used as adjuvant therapy, followed by IVIG both as monotherapy or combination therapy.³⁴ However, growing retrospective and database literature on pediatric SJS/TEN suggests lack of efficacy of corticosteroids and IVIG.³⁵ Consistent with our observations, a few of anecdotal reports have suggested etanercept as an effective treatment for pediatric patients with SJS/TEN.^{36–38} Still, the evidence is limited and further prospective randomized studies are required.

Notably, a patient with lung cancer had excellent outcomes with etanercept treatment in our study, and no tumor progression was observed during the 6-month follow-up. Immune checkpoint inhibitors have revolutionized cancer treatment. However, it has been complicated by the adverse effects known as immune-related adverse events (irAEs), including dermatologic toxicities.³⁹ A female patient with melanoma developed TEN during treatment with nivolumab. She was treated with combination therapy of prednisone, infliximab, and IVIG but unfortunately died of septic shock and multisystem organ failure.⁴⁰ Fortunately, our patient recovered from TEN. Other than the efficacy, safety is a big concern of TNF inhibitors for irAE-related SJS/TEN considering tumor progression. In our case, we did not observe any obvious tumor progression within 6 months after etanercept therapy. Further studies are required to evaluate the efficacy and safety of TNF inhibitor in treating irAE-related SJS/TEN.

As a fusion protein composed of human TNF receptor and human IgG segment, etanercept can directly bind to TNF- α and inhibit its biological activity.²⁸ We witnessed increased serum levels of TNF- α just after the initial dose of etanercept, which was consistent with previous research.^{11–13} The reduction of serum TNF- α was delayed relative to skin recovery that could be explained by the activation of TNF- α -secreting immune cells, such as macrophages. In that case, TNF- α was continuously released and sustained at a high serum level despite the skin condition was improved.¹¹ To be noted, serum level of TNF- α is potentially affected by many factors. Future studies with large samples are required to evaluate the association of serum TNF- α with multiple factors, such as the causative medicine and the therapeutic strategies.

There are some limitations to be noted. First, this is a single-center retrospective study with inherent disadvantages compared with the ideal multicenter double-blind and controlled trials. Second, we excluded patients with SJS/TEN with severe complications; thus, it is unknown whether the population would benefit from etanercept treatment. Third, there was heterogeneity of the treatment of etanercept in terms of the dosage and the time of administration. Furthermore, this study is limited by the small sample size and the incomplete data of serum level of TNF- α . Prospective randomized clinical trials are needed to further evaluate the benefits and the favorable dosing regimen of etanercept in treating SJS/TEN.

Supplementary Data

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.anai.2022.05.009>.

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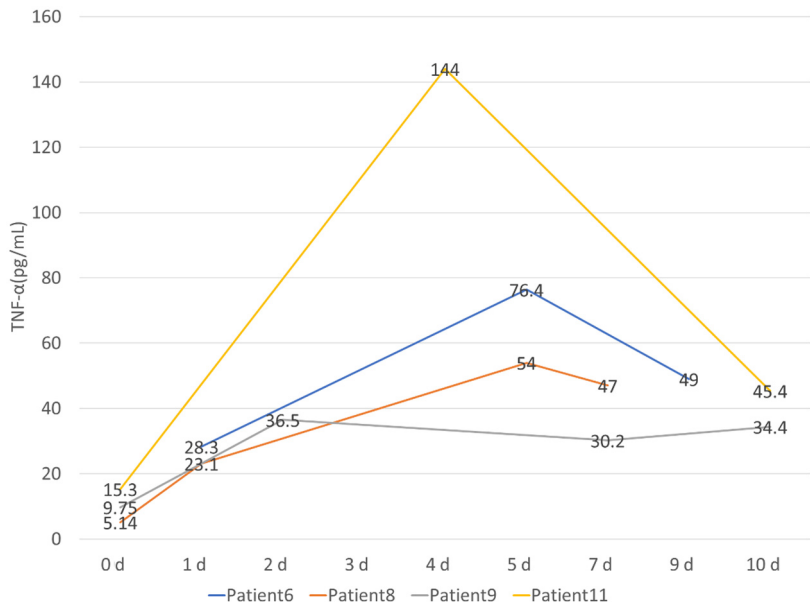
Supplementary Data

eTable 1

Serum TNF-α Levels (pg/mL) at Different Times Before and After Etanercept Injection (the Normal Range of TNF-α is 0-8.1 pg/mL)

Patient	Days										
	0 (before injection)	1	2	3	4	5	6	7	8	9	10
Patient 3			20.6			1000					
Patient 5		21.7						52.6			
Patient 6		28.3				76.4				49	
Patient 8	5.14	23.1				54		47			
Patient 9	9.75		36.5					30.2			34.4
Patient 11	15.3				144						45.4

Abbreviation: TNF-α, tumor necrosis factor alpha.



eFigure 1. Serum TNF-α levels of 4 patients at different times after etanercept injection (pg/mL). TNF-α, tumor necrosis factor-alpha.