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High Serum Level of TNF-*α* in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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Abstract

BACKGROUND: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis are severe cutaneous adverse drug reactions. Some immunological and genetic factors are believed to be involved in the pathogenesis of SJS/TEN, including tumor necrotic factor-alpha (TNF-α). Activated T-cells secrete high amounts of TNF-α and interferon-gamma that both cytokines lead to increased expression and activity of keratinocyte inducible nitric oxide synthase playing an important role in the apoptosis of keratinocytes.

AIM: This study aims to evaluate the serum level of TNF-α in SJS/TEN and the relation between it and the progress of SJS/TEN.

METHODS: This was a sectional descriptive study conducted at the National Hospital of Dermatology and Venereology, in Hanoi, Vietnam, from October 2017 to September 2019. Forty-eight SJS/TEN patients, 43 erythema multiforme (EM) patients, and 20 healthy controls (HCs) participated. TNF-α levels were measured using the fluorescence covalent microbead immunosorbent assay (FCMIA) (ProcartaPlex Immunoassay Panels kit, Thermo Fisher Scientific, USA). The Mann–Whitney U-test was used to compare serum TNF-α levels of two groups. The Wilcoxon tests were used to compare quantitative variables before and after the treatment. Differences were considered to be statistically significant at $p < 0.05$.

RESULTS: Nineteen SJS patients (39.5%) and 29 TEN patients (60.5%) participated in our study. The mean age was 49.3, range 19−77 years (47.9% of males and 52.1% of females). The most common causative drugs were traditional medicine (29.1%), carbamazepine (12.5%), and allopurinol (12.5%). On the day of hospitalization, the mean serum level of the SJS/TEN group was 32.6 pg/ml with a range from 1.3 pg/ml to 771.2 pg/ml. This level was significantly higher than that of the HCs group ($p < 0.05$) but not higher than that of the EM group. The mean serum level of TNF-α in the SJS/TEN patients on the day of hospitalization was 32.6 pg/ml, higher than that on the day of re-epithelialization (2.7 pg/ml) and the difference was statistically significant with $p < 0.05$.

CONCLUSION: Serum TNF-α levels are a good biomarker to evaluate the progress of SJS/TEN but it is not good to differentiate SJS/TEN from EM.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reactions (SCARs), often drug induced, and although rare, it is dangerous and life threatening [1]. The frequency of the disease in the population is only about 2/1,000,000 people, but the mortality rate is very high, up to 30% [2], [3], [4], [5]. The drugs commonly causing SJS/TEN are allopurinol, carbamazepine, cotrimoxazole, and abacavir [6], [7]. When the drug is present in the body, the first symptoms that appear are erythema, pruritus, localized, then more widespread, skin erosion, epidermal necrosis, and bullous formation. Mucosal lesions (mouth, eyes, nose, genitals, and anus) are common. In the eye, the lesion of the mucosa can leave sequelae such as scarring, conjunctival adhesions, and corneal ulcers [8].

The main pathophysiological feature of SJS/TEN is extensive necrosis and apoptosis of keratinocytes [9], a process initiated by drug-induced cytotoxic T lymphocytes [10], [11]. Drug presentation limited by major histocompatibility complex (MHC) or human leukocyte antigen (HLA) Class I leads to proliferation of TCD8+ [7], which infiltrates skin, and produces soluble factors that make apoptosis of keratinocytes [9], [12]. Molecules involved in apoptosis, including tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and inducible nitric oxide (NO), bridge the drug-induced immune response with damage to keratinocytes [13], [14]. Other factors such as the soluble Fas ligand (FasL) [15], perforin, and granzyme B [16] have all been emphasized in the mechanism of apoptosis of keratinocytes. Tumor necrotic factor-alpha is a potent pro-inflammatory cytokine that plays a role in many infectious and non-infectious diseases. Many cells secrete this cytokine, including immune cells (macrophages, mast cells, and T-cells) and non-immune cells (epithelial cells and keratinocytes) [17].

Erythema multiforme (EM) may have skin manifestations similar to SJS/TEN [1], [18], [19], but they can be distinguished as immunopathological. In cases of SJS/TEN, the inflammatory infiltrates expressing granulysin, granzyme B, and perforin accumulated predominantly in the lower epidermal and subepidermal bulla, in contrast, they were relatively sparse in EM [20]. However, this test is not clinically rapid. According to Morsy, serum interleukin-17 concentration in the SJS/TEN group (68.19 pg/ml) was higher than in the EM group (35.1 pg/ml) with p = 0.001 and correlated with the severity of SJS/TEN [19]. Interleukin-17 also plays an important role in the initiation and maintenance of autoimmune responses and the production of pro-inflammatory cytokines such as TNF-α [21]. Activated T-cells secrete high amounts of TNF-α and IFN-γ both cytokines lead to increased expression and activity of keratinocyte inducible nitric oxide synthase playing an important role in the apoptosis of keratinocytes [14]. We performed this study to measure the serum level of TNF-α in the SJS/TEN group, compare it with that in the EM group and the healthy controls (HCs) group, and evaluate the relation between it and the progress of SJS/TEN.

Methods

Study design and ethical clearance

This was a sectional descriptive study that had been approved by the Ethical Review Committee on Research Involving Human Subjects, Hanoi Medical University (Number 04NCS17, dated February 8, 2018). Written consent was obtained from all participants. It was conducted at the National Hospital of Dermatology and Venereology, in Hanoi, Vietnam, from October 2017 to September 2019.

Patients

In total, 48 patients with SJS/TEN were enrolled. The SJS/TEN patients had their vital signs, systemic symptoms, and the percentage of body surface area affected (skin detachment) examined. Stevens-Johnson syndrome and TEN were classified by Bastuji-Garin, based on the percentage of epidermal detachment area: (i) SJS: <10%, (ii) TEN: Greater than 30%, (iii) and overlapping SJS/TEN: 10−30% [1]. Inclusion criteria were age more than 17 years old, admission <10 days after onset (that was defined as the day mucocutaneous or ocular lesions were first eroded or ulcerated) of SJS/TEN. Exclusion criteria were human immunodeficiency virus positivity, and cases of multiorgan failure and sepsis. In addition, there were 43 EM patients and 20 HCs participating in this study as comparison groups. The SJS/TEN and EM patients were treated with systemic corticosteroids at the dose of 1−2 mg prednisolone/kg/day in combination with care support.

Analysis cytokines

For 48 SJS/TEN patients, we took blood samples at 2 time points: (1) On the day of hospitalization and (2) on the day of re-epithelialization. For EM patients and HCs, the blood was taken at one point, before the treatment. All blood samples were left to coagulate at room temperature for 10−20 min, then centrifuged for 20 min at a speed of 2000−3000 r.p.m, finally, serum was taken and stored at −80°C until proceeding the cytokine measurement. We measured serum TNF-α levels using the fluorescence covalent microbead immunosorbent assay (FCMIA) (ProcartaPlex Immunoassay Panels kit, Thermo Fisher Scientific, USA).

Statistical analysis

Data entry and analysis were conducted using SPSS software version 16.0 (IBM, Armonk, NY, USA). The Mann–Whitney U-test was used to compare serum TNF-α levels of two groups. The Wilcoxon tests were used to compare quantitative variables before and after the treatment of the SJS/TEN group. Differences were considered to be statistically significant at $p < 0.05$.

Results

Nineteen SJS patients (39.5%) and 29 TEN patients (60.5%) participated in our study. Their characteristics are shown in Table 1. The mean age was 49.3, range 19−77 years (47.9% of males and 52.1% of females). The most common causative drugs were traditional medicine (29.1%), carbamazepine (12.5%),

Table 1: Characteristics of Stevens-Johnson syndrome/toxic epidermal necrolysis patients

Characteristics	Results
Classification, *n* (%)	
SJS	19 (39.5)
TEN	29 (60.5)
Age, years	49.3 ± 15.0
Sex, n (%)	
Male	23 (47.9)
Female	25 (52.1)
Causative drugs, n (%)	
Traditional medicine	14 (29.1)
Carbamazepine	6 (12.5)
Allopurinol	6 (12.5)
Antibiotics	3 (6.2)
NSAIDs	4 (8.4)
Thalidomide	1 (2.1)
Unknown	14 (29.2)
The time between onset and hospitalization, days	5.9 ± 2.7
Body surface area affected, %	43.7 ± 34.7
Fever, n (%)	27 (56.2)
Mucous membrane lesions	39 (81.2)
Pneumonia	8 (16.7)
The time of re-epithelialization, days	15.9 ± 4.6

SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, NSAIDs: Nonsteroidal anti-inflammatory drugs.

and allopurinol (12.5%). The time between the onset and the day of hospitalization was 5.9 days (range 2−18 days). The mean body surface area affected was 43.7%. The percentage of fever, mucous membrane lesions, and pneumonia were 56.2%; 81.2%, and 16.7%, respectively. The mean time of re-epithelialization was 15.9 days (range 9−31 days). All SJS/TEN patients got re-epithelialization and total resolution, and no one with in-hospital mortality.

Table 2: The serum levels of tumor necrotic factor-alpha in Stevens-Johnson syndrome/toxic epidermal necrolysis, erythema multiforme, and healthy controls groups

Serum level of TNF-α (pg/ml)	SJS/TEN (n = 48)	EM (n = 43)	HCs (n = 20)	p (Mann–Whitney U-test)
Mean ± SD	32.6 ± 125	7.6 ± 26.9	27.7 ± 37.9	p1 > 0.05
Media	1.3	1.3	6	p2 < 0.05
Range	1.3-771.2	1.3-172.4	1.3-109.3	p3 > 0.05

p1: SJS/TEN versus EM, p2: SJS/TEN versus HCs, p3: EM versus HCs. TNF-α: Tumor necrotic factor-alpha, EM: Erythema multiforme, HCs: Healthy controls, SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, SD: Standard deviation.

On the day of hospitalization, the mean serum TNF-α level of the SJS/TEN group was 32.6 pg/ml with a range from 1.3 pg/ml to 771.2 pg/ml. This level was significantly higher than that of the HCs group ($p < 0.05$) but not higher than that of the EM group (as shown in Table 2 and Figure 1).

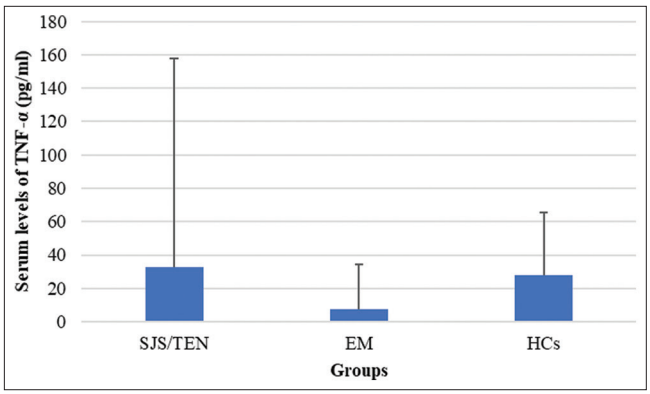

Figure 1: Serum levels of TNF-α in SJS/TEN, EM, and HCs groups

The mean serum level of TNF-α in the SJS/TEN patients with the onset of fewer than 6 days was 5.7 ± 170.7 pg/ml, not higher than that of patients with the onset of more than 6 days (5.8 ± 10.7 pg/ml), $p > 0.05$ (Mann–Whitney U-test), as shown in Table 3 and Figure 2.

Table 3: Serum levels of tumor necrotic factor-alpha in Stevens-Johnson syndrome/toxic epidermal necrolysis group following the day of onset

Serum level of TNF-α (pg/ml)	The day of onset		p (Mann–Whitney U-test)
	< 6 days (n = 25)	≥ 6 days (n = 23)	
Mean ± SD	5.7 ± 170.7	5.8 ± 10.7	>0.05
Media	1.3	1.3	
Range	1.3–771.2	1.3–47.5	

TNF-α: Tumor necrotic factor-alpha, SD: Standard deviation.

The mean serum level of TNF-α in the SJS/TEN patients using systemic corticosteroids before hospitalization was 50.8 pg/ml, higher than that of the SJS/TEN patients without using (24.7 pg/ml) but the difference was not statistically significant with $p > 0.05$ (Mann–Whitney U-test), as shown in Table 4 and Figure 3.

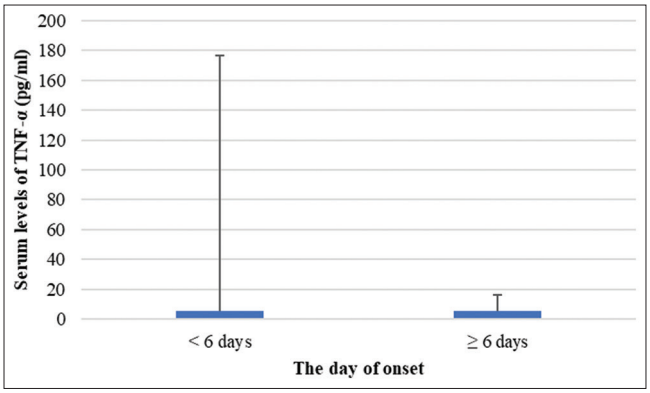

Figure 2: Serum levels of TNF- α in SJS/TEN group following the day of onset

The mean serum level of TNF-α in the SJS/TEN patients on the day of hospitalization was 32.6 pg/ml, higher than that on the day of re-epithelialization (2.7 pg/ml) and the difference was statistically significant with $p < 0.01$ (Wilcoxon test), as shown in Table 5 and Figure 4.

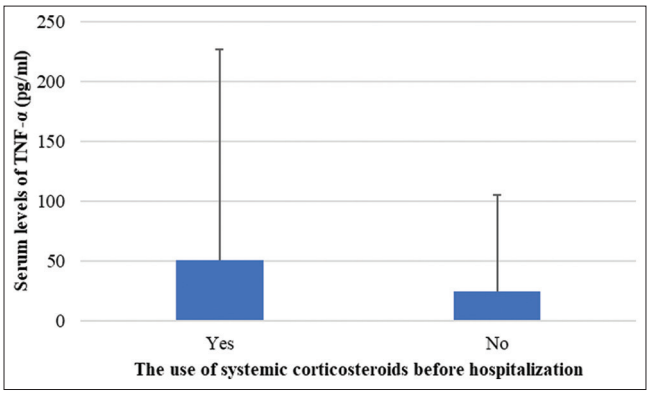

Figure 3: Serum levels of TNF-α in SJS/TEN group following the use of systemic corticosteroids before hospitalization

Discussion

In our study, the TNF-α concentration of the SJS/TEN group was significantly higher than that of the HCs group ($p < 0.05$) but not higher than that of the EM group ($p > 0.05$). After treatment, when re-epithelialization was completed, the TNF-α concentration was only 2.7 pg/ml, much lower than that on the day of hospitalization, the

Table 4: Serum levels of tumor necrotic factor-alpha in Stevens-Johnson syndrome/toxic epidermal necrolysis group following the use of systemic corticosteroids before hospitalization

Serum level of TNF-α (pg/ml)	The use of systemic corticosteroids before hospitalization		p (Mann–Whitney U-test)
	Yes (n = 20)	No (n = 21)	
Mean ± SD	50.8 ± 176.2	24.7 ± 80.7	> 0.05
Media	1.3	1.3	
Range	1.3–771.2	1.3–373.2	

TNF-α: Tumor necrotic factor-alpha, SD: Standard deviation.

difference was statistically significant with p < 0.01. The serum TNF-α concentration in this study was lower than that in Su's study [3] but higher than that in Wang's study [22]. According to Su's study, the concentration of TNF-α in the SJS/TEN patients that excluded sepsis was 58.2 pg/ml, and in the group that did not exclude sepsis was 98.1 pg/ml. Patients were diagnosed with sepsis based on blood cultures or blood procalcitonin >2 ng/ml [3].

Table 5: Serum levels of tumor necrotic factor-alpha in Stevens-Johnson syndrome/toxic epidermal necrolysis patients on the day of hospitalization and the day of re-epithelialization

Serum level of TNF-α (pg/ml)	The day of hospitalization (n = 48)	The day of re-epithelialization (n = 48)	p (Wilcoxon test)
Mean ± SD	32.6 ± 125	2.7 ± 7.9	< 0.01
Media	1.3	1.3	
Range	1.3–771.2	1.3–55.2	

TNF-α: Tumor necrotic factor-alpha, SD: Standard deviation.

In our study, no patient had such an infection. Along with interleukine-6 and interleukine-1, TNF-α is a cytokine with a key role in sepsis [17]. Wang's study measured TNF-α levels in the serum and the bullous fluid of 27 SJS/TEN patients using the ELISA method. The mean serum TNF-α concentration of patients in the acute phase of SJS/TEN was 3.33 pg/ml and that in the remission phase was 2.53 pg/ml. The mean concentration of TNF-α in the bullous fluid of six patients with SJS/TEN was 13.4 pg/ml, which was higher than that in the serum [22]. Thus, the concentration of TNF-α increases during the acute phase of SJS/TEN, which initiates the disease, and decreases during the remission phase. Research on the role of TNF-α may open up new therapeutic avenues, using biological agents against TNF-α in SJS/TEN, as in psoriasis [23], [24] and rheumatoid arthritis [25], [26].

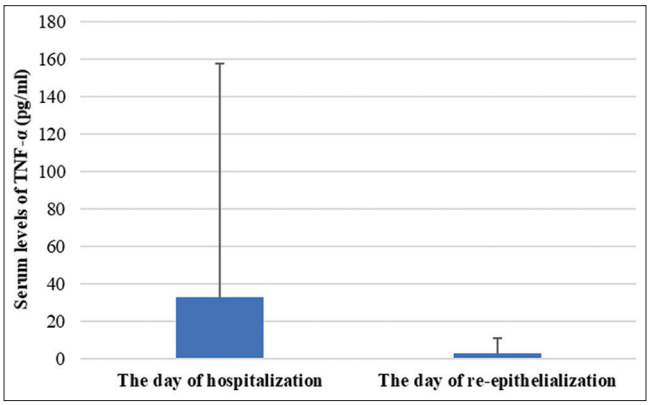

Figure 4: Serum levels of TNF- α in SJS/TEN group on the day of hospitalization and the day of re-epithelialization

The review study by Zhang *et al*. (2020) showed that anti-TNF-α agents are used as monotherapy, second-line therapy, or in combination in the treatment of SJS/TEN. Research articles on the use of anti-TNF-α in the treatment of SJS/TEN are mainly case reports (21 articles), case series (four articles), and only two randomized controlled trials. There were 86.8% of patients (79/91) had a good response, few side effects, and complications [27]. There have been reports of an 11-year-old child with sulfamethoxazole-trimethoprim-associated SJS who responded slowly to methylprednisolone plus cyclosporine, whose disease progression ceased when an anti-TNF-α regimen was added [28]. This therapy has the advantage that a single dose can be used. Paradisi reported 10 patients with SJS/TEN treated with etanercept (anti-TNF-α) with a single dose of 50 mg subcutaneously. The study did not have a control group. All patients responded well, the mean time of re-epithelialization was 8.5 days. Although the SCORTEN (SCORe of Toxic Epidermal Necrolysis) estimated that mortality rate was 50%, no patient died [29]. In this study, no patient was treated with an anti-TNF-α regimen because systemic corticosteroids in combination with care support still revealed a good response, not only to clinical symptoms but also in reducing serum TNF-α. Hirahara *et al*. showed that on day 4 after methylprednisolone administration, mean levels of IFN-γ, TNF-α, IL-6, and IL-10 were decreased compared with pre-administration levels (day 0), but only changes in IFN-γ and IL-6 reached statistical significance [30].

Overexpression of TNF-α derived from macrophages and keratinocytes in lesions of TEN indicates a link between TNF-α and extensive necrosis in TEN. Tumor necrotic factor-alpha is also a cytokine that induces apoptosis, activation, and differentiation of cells and causes inflammation. On binding to surface receptors, TNF-α activates apoptosis through activation of the caspase cascade, altering mitochondria, leading to various toxic processes, including the production of free radicals and the attack of deoxyribonucleic acid (DNA) by the endonuclease. In addition to the activation of apoptosis, in the pathogenesis of SJS/TEN, TNF-α also exerts an effect on the inflammatory response. It alters the permeability of vascular endothelial cells and the interaction between leukocytes and vascular endothelial cells. When coexpressing cell-specific adhesion molecules, TNF-α mobilizes different populations of immune cells. The histopathological picture of SJS/TEN is predominantly leukocyte infiltration, possibly due to chemotaxis caused by TNF-α [12].

This study had some limitations. First, we collected serum samples several days after the onset of SJS/TEN when serum TNF-α levels might have been decreased a lot, some patients were already treated with systemic corticosteroid before hospitalization. Second, we only measured TNF-α levels in sera and were not able to quantify them in blister fluids and identify the presence of TNF-α on skin tissue. However, the mean serum level of TNF-α in the SJS/TEN patients with the onset of fewer than 6 days was not higher than that of patients with the onset of more than 6 days. The mean serum level of TNF-α in the SJS/TEN patients using systemic corticosteroids before hospitalization was higher than that of the SJS/TEN patients without using but the difference was not statistically significant. This may be due to the that, in the early and acute

phase of SJS/TEN, the inflammatory response is strong, and TNF-α is produced so much, even that, systemic corticosteroids could not reduce its serum level immediately.

Conclusion

Serum TNF-α level in SJS/TEN patients is higher than those in HCs. It is also a good biomarker to evaluate the progress of SJS/TEN but it is not good to differentiate SJS/TEN from EM.

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