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Serum Levels of Interleukin-1 Beta are Decreased in Patients with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis at the Time of Hospitalization

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Abstract

BACKGROUND: Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reactions. Some immunological and genetic factors are believed to be involved in the pathogenesis of the disease, including tumor necrotic factor-alpha, interferon-gamma, and interleukin (IL)-17. IL-1β is one of the most prominent cytokines associated with the innate immune response.

AIMS: The study aimed to evaluate the serum level of IL-1β in SJS/TEN and the relation between it and the progress of SJS/TEN.

METHODS: This was a cross-sectional descriptive study conducted at the National Hospital of Dermatology and Venereology, in Hanoi, Vietnam, from October 2017 to September 2019. 48 SJS/TEN patients, 43 erythema multiforme (EM) patients, and 20 healthy controls (HCs) participated. IL-1β levels were measured using the fluorescence covalent microbead immunosorbent assay (ProcartaPlex Immunoassay Panels kit, Thermo Fisher Scientific, USA). The Mann–Whitney U test was used to compare serum IL-1β levels. 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: 19 SJS patients (39.5%) and 29 TEN patients (60.5%) participated in our study. The mean age was 49.3 years; the range was 19–77 years (47.9% males; 52.1% 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 IL-1β of the SJS/TEN group was 26.4 ± 81.7 pg/mL, ranging from 0.5 pg/mL to 447 pg/mL. This level was significantly lower than that of the HCs group ($p < 0.001$) but not lower than that of the EM group. The mean serum level of IL-1β in the SJS/TEN patients on the day of hospitalization was 26.4 ± 81.7 pg/ml, higher than that on the day of re-epithelialization (1.9 ± 5.6 pg/mL) and the difference was statistically significant with $p < 0.01$.

CONCLUSION: Serum IL-1β level in SJS/TEN patients is lower than in HCs. It is not a good biomarker to differentiate SJS/TEN from EM.

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reactions, often drug-induced and, although rare, they are dangerous and potentially fatal [1]. The rate of occurrence of the illness in the population is only about 2 in every 1,000,000 people, but it has an extremely high fatality rate of up to 30% [2], [3], [4], [5]. The drugs commonly causing SJS/TEN are allopurinol, carbamazepine, cotrimoxazole, and abacavir [6], [7]. The initial symptoms of the drug's presence in the body include erythema, pruritus, localized, then more widespread, skin erosion, epidermal necrosis, and bullous formation. It's typical to develop mucosal lesions in the mouth, eyes, nose, genitals, and anus. The mucosal lesion in the eye 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]. Major histocompatibility complex or human leukocyte antigen class I-restricted drug presentation causes TCD8+ proliferation [7], which infiltrates skin, and produces soluble factors that result in apoptosis of keratinocytes [9], [12]. Apoptosis-related molecules, including tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and inducible nitric oxide (NO), serve as intermediaries connecting the drug-induced immune response with damage to keratinocytes [13], [14]. Other factors such as the soluble fas ligand [15], perforin, and granzyme B [16] have all been emphasized in the mechanism of apoptosis of keratinocytes.

Interleukin (IL)-1α, IL-1β, IL-6, IL-18, IL-33, and TNF are the most prominent cytokines associated with the innate immune response. These cytokines

can act both locally and systemically [17]. TNF-α is a potent pro-inflammatory cytokine that plays a role in many infectious and non-infectious diseases. This cytokine is secreted by many cells, including immune cells (macrophages, mast cells, T cells) and non-immune cells (epithelial cells, keratinocytes) [18]. Erythema multiforme (EM) may have skin symptoms resembling those of SJS/TEN [1], [19], [20], but they can be set apart through their immunopathological characteristics. In cases of SJS/TEN, the inflammatory infiltrates that express granulysin, granzyme B, and perforin are primarily concentrated within the lower epidermal and subepidermal bulla. Conversely, they were less abundant in EM [21]. However, this test is not clinically rapid. According to Morsy, serum IL-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 [20]. IL-17 also has a crucial function in triggering and sustaining autoimmune responses and generating pro-inflammatory cytokines like TNF-α [22]. Activated T cells secrete high amounts of TNF-α and IFN-γ. Both cytokines lead to elevated expression and activity of keratinocyte inducible NO synthase, which plays a key role in keratinocyte apoptosis [14]. We performed this study to measure the serum level of IL-1β in the SJS/TEN group, compare it with that in the EM group and the healthy controls (HCs) group, and evaluate the relationship between it and the progress of SJS/TEN.

Methods

Study design and ethical clearance

This was a cross-sectional descriptive study that had been approved by the ethical review committee on research involving human subjects, Hanoi Medical University (Number 04NCS17, dated February 8th, 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. SJS and TEN were classified by Bastuji-Garin [1], based on the percentage of epidermal detachment area: (i) SJS: <10%, (ii) TEN: >30%, iii) and overlapping SJS/TEN: 10–30% [1]. Inclusion criteria were age more than 17 years old, and 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 multi-organ failure and sepsis. In addition, 43 EM patients and 20 HCs participated 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 two 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 with the cytokine measurement. We measured serum IL-1β levels using the fluorescence covalent microbead immunosorbent assay (ProcartaPlex Immunoassay Panels kit, Thermo Fisher Scientific, USA).

Statistical analysis

Data entry and analysis were conducted using the SPSS software version 16.0 (IBM, Armonk, NY, USA). The Mann–Whitney U test was used to compare serum IL-1β levels of the 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

Table 1: Characteristics of SJS/TEN patients

Characteristics	n (%)
Classification	
SJS	19 (39.5)
TEN	29 (60.5)
Age/years	49.3 ± 15.0
Sex	
Male	23 (47.9)
Female	25 (52.1)
Causative drugs	
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/day	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/day	15.9 ± 4.6

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

49.3 years, range 19–77 years (47.9% males; 52.1% females). The most common causative drugs were traditional medicine (29.1%), carbamazepine (12.5%), 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.

On the day of hospitalization, the mean serum IL-1β level of the SJS/TEN group was 26.4 ± 81.7 pg/ml, ranging from 0.5 pg/mL to 447 pg/mL. This level was significantly lower than that of the HCs group ($p < 0.001$) but not lower than that of the EM group ($p > 0.05$), as shown in Table 2.

Table 2: The serum levels of IL-1β in SJS/TEN, EM, and HCs groups

Serum level of IL-1β (pg/mL)	SJS/TEN (n = 48)	EM (n = 43)	HCs (n = 20)	p (Mann–Whitney U test)
Mean ± standard deviation	26.4 ± 81.7	33 ± 179	98.6 ± 130.6	p1 > 0.05
Median	0.5	0.5	43.5	p2 < 0.001
Range	0.5–447	0.5–1174.1	0.5–405.9	p3 < 0.05

SJS: Stevens–Johnson syndrome, TEN: Toxic epidermal necrolysis, P1: SJS/TEN versus EM, P2: SJS/TEN versus HCs, P3: EM versus HCs, HCs: Healthy controls, EM: Erythema multiforme.

The mean serum level of IL-1β in the SJS patients was 35.8 ± 81.4 pg/mL, higher than that of the TEN patients (20.3 ± 82.7 pg/mL) but the difference was not statistically significant with $p > 0.05$, as shown in Table 3.

Table 3: The serum levels of IL-1β in SJS and TEN groups

Serum level of IL-1β (pg/mL)	SJS (n = 19)	TEN (n = 29)	p (Mann–Whitney U test)
Mean ± standard deviation	35.8 ± 81.4	20.3 ± 82.7	> 0.05
Median	1.1	0.5	
Range	0.5–330.3	0.5–447	

SJS: Stevens–Johnson syndrome; TEN: Toxic epidermal necrolysis

The mean serum level of IL-1β in the SJS/TEN patients with the onset of fewer than 6 days was 40.3 ± 110.4 pg/mL, not higher than that of patients with the onset of more than 6 days (11.3 ± 22 pg/mL), $p > 0.05$, as shown in Table 4.

Table 4: Serum levels of IL-β in the SJS/TEN group following the day of onset

Serum level of IL-β (pg/mL)	The day of onset		p (Mann–Whitney U test)
	< 6 days (n = 25)	≥ 6 days (n = 23)	
Mean ± standard deviation	40.3 ± 110.4	11.3 ± 22	> 0.05
Median	0.5	0.5	
Range	0.5–447	0.5–89.5	

The mean serum level of IL-1β in the SJS/TEN patients using systemic corticosteroids before hospitalization was 26 ± 79.3 pg/mL, lower than that of the SJS/TEN patients without using (32.4 ± 97.5 pg/mL) but the difference was not statistically significant with $p > 0.05$, as shown in Table 5.

The mean serum level of IL-1β in the SJS/TEN patients on the day of hospitalization was 26.4 ± 81.7 pg/mL, higher than that on the day of re-epithelialization (1.9 ± 5.6 pg/mL) and the difference was statistically significant with $p < 0.01$, as shown in Table 6.

Table 5: Serum levels of IL-β in the SJS/TEN group following the use of systemic corticosteroids before hospitalization

Serum level of IL-β (pg/mL)	The use of systemic corticosteroids before hospitalization		p (Mann–Whitney U test)
	Yes (n = 20)	No (n = 21)	
Mean ± standard deviation	26 ± 79.3	32.4 ± 97.5	>0.05
Median	0.5	0.5	
Range	0.5–330.3	0.5–447	

Table 6: Serum levels of IL-β in SJS/TEN patients on the day of hospitalization and the day of re-epithelialization

Serum level of IL-β (pg/mL)	The day of hospitalization (n = 48)	The day of re-epithelialization (n = 48)	p (Wilcoxon test)
Mean ± standard deviation	26.4 ± 81.7	1.9 ± 5.6	< 0.01
Median	0.5	0.5	
Range	0.5–477	0.5–32.8	

Discussion

IL-1β is produced by monocytes, macrophages, Langerhans cells, and dendritic cells; IL-1α is produced by epithelial cells, including keratinocytes. IL-1α is stored in the cytoplasm. When cells are damaged, biologically active 31-kDa IL-1α is released, causing an inflammatory response. IL-1β stimulates Langerhans cells to migrate from the epidermis during the early stages of a contact hypersensitivity reaction, leading to Langerhans cell infiltration in lymph nodes [22].

The serum concentration of IL-1β of the SJS/TEN group in this study was not different from the EM group but was lower than the HCs group ($p < 0.001$), with no difference between the SJS group and the TEN group. However, IL-1β concentration on the day of re-epithelialization decreased, much lower than that on the day of hospitalization ($p < 0.01$). This can be explained by the fact that IL-1β is released by necrotic keratinocytes during the progression of SJS/TEN. By the time re-epithelialization occurs, all necrotic keratinocytes have fallen off. The role of IL-1β in SJS/TEN is unclear, because in the HCs group the serum concentration of this cytokine was much higher than that in the SJS/TEN group. Normally, healthy keratinocytes may produce and store more IL-1β than diseased necrotic keratinocytes.

IL-1α and IL-1β are initially synthesized as precursor proteins and subsequently undergo proteolytic cleavage. In opposition to IL-1β, full-length IL-1α exhibits inherent biological activity. Ca^{++}-dependent proteases such as calpains perform cleavage of IL-1α [23]; however, the reason and benefit of this cleavage is still debated. IL-1β is yet much better characterized. Together with IL-1α, it is expelled from the cell at the initial stages of inflammation and, initially, induces localized inflammation and, eventually,

systemic inflammation and fever. Both IL-1α and IL-1β share IL-1R1 as their common receptor. IL-1 receptor activation plays a pivotal role in the induction of fever. Dinarello administered a few nanograms of IL-1 intravenously to individuals in good health which resulted in fever, leukocytosis, and hypotension [24]. In the last decade, however, we learned that IL-1β does not only mediate fever but also plays a role in various organ systems. This includes its involvement in processes like tumor angiogenesis within the vascular system [25], as well as conditions such as rheumatoid arthritis, osteoarthritis [26], and even diabetes, where IL-1 receptor blockade serves as an effective treatment option [27]. Due to their high biological impact and efficacy, transcription, synthesis, and secretion of both IL-1α and IL-1β are tightly regulated. However, in specific resident cells such as keratinocytes, IL-1α and IL-1β are present on both cDNA and protein levels at baseline [28], [29], [30], the transcriptional activation of these cytokines is required in myeloid cells such as macrophages, monocytes, and dendritic cells [31].

This study had some limitations. First, we collected serum samples several days after the onset of SJS/TEN when serum IL-1β levels might have decreased a lot, some patients were already treated with systemic corticosteroids before hospitalization. Second, we only measured IL-1β levels in sera and were not able to quantify them in blister fluids and identify the presence of IL-1β in skin tissue. However, the mean serum level of IL-1β 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 IL-1β in the SJS/TEN patients using systemic corticosteroids before hospitalization was lower than that of the SJS/TEN patients who did not use systemic corticosteroids but the difference was not statistically significant.

Conclusion

The limit of this study is late sample collection. Hence, serum IL-1β level in SJS/TEN patients is lower than that in HCs. It is not a good biomarker to differentiate SJS/TEN from EM.

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