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Serum Concentrations of $T_{helper}2$-derived Cytokines in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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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 SJS/TEN, including $T_{helper}1$ and $T_{helper}2$ (Th2)-derived cytokines.

AIM: This study aims to evaluate the serum levels of Th2-derived cytokines in SJS/TEN, compare to those of erythema multiforme (EM) patients, and the relation between them 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. 48 SJS/TEN patients, 43 EM patients, and 20 healthy controls (HCs) participated. Serum interleukin (IL)-4, IL-5, and IL-13 levels were measured by 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 the serum IL levels of the 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: 19 SJS patients (39.5%) and 29 TEN patients (60.5%) participated in our study. The mean age was 49.3, range of 19–77 years (47.9% males; 52.1% females). The most common causative drugs were traditional medicine (29.1%), and allopurinol (12.5%). On the day of hospitalization, the serum level of IL-4 in the SJS/TEN group was 3 ± 7.5 pg/mL, statistically significantly higher than that in the HCs group ($p < 0.05$), but not higher than that in the EM group ($p > 0.05$); serum levels of IL-5 and IL-13 in the SJS/TEN group were 4.5 ± 9.8 pg/mL and 1.6 ± 0.6 pg/mL, respectively, similar to those in the EM and HCs groups. On the day of re-epithelialization, in SJS/TEN patients, the serum level of IL-5 was 1 ± 2.8 pg/ml, statistically significantly lower than that on the day of hospitalization (3 ± 7.5 pg/mL) with $p < 0.05$. Regarding serum levels of IL-4 and IL-13, there was no difference between the two-time points.

CONCLUSION: The serum concentrations of Th2-derived cytokines (IL-4, IL-5, and IL-13) were not higher in the SJS/TEN group than in the EM group and there was no significant change in the clinical progression of SJS/TEN, except the serum level of IL-5.

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reactions, often drug-induced. Although rare, they are dangerous and life-threatening. 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 most 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 lesions of the mucosa can leave sequelae such as scarring, conjunctival adhesions, and corneal ulcers [8].

The main pathophysiological feature of SJS/TEN is extensive apoptosis and necroptosis of keratinocytes [9], a process initiated by drug-induced cytotoxic T lymphocytes [10], [11]. Drug presentation limited by major histocompatibility complex or human leukocyte antigen class I leads to the proliferation of TCD8+ [7], which infiltrates the skin, producing soluble factor that causes keratinocytes apoptosis [9], [12]. Molecules involved in apoptosis, including tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and inducible nitric oxide (NO), are bridging the drug-induced immune response with damage to keratinocytes [13], [14]. Factors such as the soluble Fas ligand (FasL), perforin, and granzyme B16 are all emphasized in the apoptosis mechanism of keratinocytes [15], [16].

Previous studies have shown that in SJS/TEN, there is an increase in serum levels of $T_{helper}1$ (Th1)-derived interleukins (ILs) such as TNF-α [17] or

IFN-γ [18]. This study aimed to investigate serum levels of $T_{helper}2$ (Th2)-derived cytokines (IL-4, IL-5, and IL-13) and their association with the clinical progression of SJS/TEN.

Methods

Study design and ethical clearance

This cross-sectional descriptive study was approved by the Ethical Review Committee on Research Involving Human Subjects, Hanoi Medical University (Number 04NCS17, dated 8th February 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, 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 erythema multiforme (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-4, IL-5, and IL-13 levels by 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 the two groups' serum IL-4, IL-5, and IL-13 levels. 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

In the SJS/TEN group, the mean age was 49.3; males accounted for 47.9%; females accounted for 52.1%. Cause of SJS/TEN due to traditional medicine accounts for 29.1%; due to allopurinol accounting for 12.5%; due to antibiotics accounting for 6.2%; unknown cause accounted for 29.2%. There were 81.2% of patients with mucosal lesions. In the EM group, the mean age was 41.4 (ranging from 19 to 76 years old), male accounted for 30.2%, female accounted for 69.8%; drug-induced causes accounted for 41.9%, unknown cause 58.1%. The EM patients had atypical target lesions (69.7%), typical (16.3%), and both types (14%); the rate of mucosal lesions was 20.9%, and fever was 23.3%. The average age of HCs was 28.4 (25–37 years old), 50% male and 50% female (Table 1).

Table 1: Characteristics of participants

Characteristics	EM (n = 43)	HCs (n = 20)	SJS/TEN (n = 48)
Age (year)			
Mean ± SD	41.4 ± 17.3	28.4 ± 3.5	49.3 ± 15.0
Range	19–76	25–37	19–77
Gender, n (%)			
Male	13 (30.2)	10 (50)	23 (47.9)
Female	30 (69.8)	10 (50)	25 (52.1)
Causes, n (%)		NA	
Medicine	18 (41.9)		
Traditional medicine	8 (44.4)		14 (29.1)
Antibiotics	5 (27.8)		3 (6.2)
Allopurinol	3 (16.6)		6 (12.5)
Herbal food	2 (11.2)		0
Unknown	25 (58.1)		14 (29.2)
Cutaneous lesions, n (%)		NA	NA
Typical target lesions	7 (16.3)		
Atypical target lesions	30 (69.7)		
Both typical and atypical lesions	6 (14)		
Mucous lesions, n (%)	9 (20.9)	NA	39 (81.2)
Fever, n (%)	10 (23.3)	NA	27 (56.2)

SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, NSAIDs: Nonsteroid anti-inflammatory drugs, NA: Nonapplicable, SD: Standard deviation, EM: Erythema multiforme, HCs: Healthy controls.

The serum level of IL-4 in the SJS/TEN group was 3 ± 7.5 pg/mL, statistically significantly higher than that in the HCs group ($p < 0.05$), but not higher than that in the EM group ($p > 0.05$). Serum levels of IL-5 and IL-13 in the SJS/TEN group were 4.5 ± 9.8 pg/mL and 1.6 ± 0.6 pg/mL, respectively, similar to those in the EM and HCs groups (Table 2).

In the SJS group, serum levels of IL-4, IL-5, and IL-13 were 4.1 ± 6.7 pg/mL; 6.5 ± 11.5 pg/mL, and 1.6 ± 0.3 pg/mL, respectively. They were not different from those of the TEN group (Table 3).

In SJS/TEN patients having the onset under 6 days, serum levels of IL-4, IL-5, and IL-13 were

Table 2: The serum levels of interleukin-4, interleukin-5, and interleukin-13 (pg/mL) in Stevens-Johnson syndrome/toxic epidermal necrolysis, erythema multiforme, and healthy controls groups

Cytokine (pg/mL)	SJS/TEN (n = 48)	EM (n = 43)	HCs (n = 20)	p (test Mann–Whitney U)
IL-4				
Mean ± SD	3 ± 7.5	1.6 ± 4.1	2.5 ± 3	p1 > 0.05
Median	0.8	0.8	0.8	p2 < 0.05
Range	0.8–43.8	0.8–25.8	0.8–9	p3 > 0.05
IL-5				
Mean ± SD	4.5 ± 9.8	6.9 ± 18.5	8.2 ± 14.5	p1 > 0.05
Median	0.5	0.5	0.5	p2 > 0.05
Range	0.9–43.8	0.5–92.9	0.5–37.4	p3 > 0.05
IL-13				
Mean ± SD	1.6 ± 0.6	1.5	1.5	p1 > 0.05
Median	1.5	1.5	1.5	p2 > 0.05
Range	1.5–5.1	1.5–1.5	1.5–1.5	p3 > 0.05

p1: The SJS/TEN group versus the EM group, p2: The SJS/TEN group versus the HCs group, p3: The EM group versus the HCs group. SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, SD: Standard deviation, EM: Erythema multiforme, HCs: Healthy controls, IL: Interleukin.

4.4 ± 9.8 pg/mL; 6 ± 12.5 pg/mL, and 1.6 ± 0.7 pg/mL, respectively. They were not different from those in SJS/TEN patients having the onset from 6 days and more (Table 4).

Table 3: Comparing serum levels of interleukin-4, interleukin-5, and interleukin-13 (pg/mL) between the Stevens-Johnson syndrome group and the toxic epidermal necrolysis group

Cytokine (pg/mL)	SJS (n = 19)	TEN (n = 29)	p (test Mann–Whitney U)
IL-4			
Mean ± SD	4.1 ± 6.7	2.3 ± 8	>0.05
Median	0.8	0.8	
Range	0.8–22	0.8–43.9	
IL-5			
Mean ± SD	6.5 ± 11.5	3.2 ± 8.4	>0.05
Median	0.5	0.5	
Range	0.5–42.6	0.9–43.8	
IL-13			
Mean ± SD	1.6 ± 0.3	1.6 ± 0.7	>0.05
Median	1.5	1.5	
Range	1.5–3	1.5–5.1	

SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, SD: Standard deviation, IL: Interleukin.

On the day of re-epithelialization, in SJS/TEN patients, the serum level of IL-5 was 1 ± 2.8 pg/ml, statistically significantly lower than that on the day of hospitalization (3 ± 7.5 pg/mL) with $p < 0.05$. Regarding serum levels of IL-4 and IL-13, there was no difference between the two-time points (Table 5).

Table 4: Serum levels of interleukin-4, interleukin-5, and interleukin-13 (pg/mL) in the Stevens-Johnson syndrome/toxic epidermal necrolysis group following the day of onset

Cytokine (pg/mL)	The day of onset		p (test Mann–Whitney U)
	< 6 days (n = 25)	≥ 6 days (n = 23)	
IL-4			
Mean ± SD	4.4 ± 9.8	1.4 ± 3.1	>0.05
Median	0.8	0.8	
Range	0.8–43.8	0.8–15.6	
IL-5			
Mean ± SD	6 ± 12.5	2.9 ± 5.2	>0.05
Median	0.5	0.5	
Range	0.5–43.9	0.5–17.4	
IL-13			
Mean ± SD	1.6 ± 0.7	1.5 ± 0.31	>0.05
Median	1.5	1.5	
Range	1.5–5.1	1.5–3	

SD: Standard deviation, IL: Interleukin.

Discussion

IL-4 and IL-13 are produced by activated Th2 cells, they are about 30% similar in structure but have different biological activities. The IL-4-specific receptor that does not bind to IL-13 is found in T cells and natural killer (NK) cells. These include IL-4Rα (CD124) and γc, which transmit signals through Janus kinase 1 (JAK1) and JAK3. A second receptor complex that can bind either IL-4 or IL-13 is found in keratinocytes, endothelial cells, and other non-hematopoietic cells. It consists of IL-13α1 and IL-4Rα, which transmit signals through JAK1 and JAK2. These receptors are less expressed in resting cells but are increased in the presence of activation signals [19].

Table 5: Serum levels of interleukin-4, interleukin-5, and interleukin-13 (pg/mL) in Stevens-Johnson syndrome/toxic epidermal necrolysis patients on the day of hospitalization and the day of re-epithelialization

Cytokine (pg/mL)	The day of hospitalization (n = 48)	The day of re-epithelialization (n = 48)	p (test Wilcoxon)
IL-4			
Mean ± SD	3 ± 7.5	1.1 ± 2.1	>0.05
Median	0.8	0.8	
Range	0.8–43.8	0.8–15.6	
IL-5			
Mean ± SD	4.5 ± 9.8	1 ± 2.8	<0.05
Median	0.5	0.5	
Range	0.9–43.8	0.5–19.3	
IL-13			
Mean ± SD	1.6 ± 0.6	1.5 ± 0	>0.05
Median	1.5	1.5	
Range	1.5–5.1	1.5–1.5	

SD: Standard deviation, IL: Interleukin.

The biological effects of IL-4 upon binding to various receptors are cell type-specific, but the main effect is stimulation of Th2 growth and differentiation and inhibition of Th1 [20]. Exposure of naive T cells to IL-4 helps them mature and differentiate into Th2, producing more IL-4, which induces local stimulation, prolonging the response time of Th2. Thus, early expression of IL-4 in the immune response may initiate the Th2 developmental cascade, which predominates the Th2 response. Naive T cells can produce low levels of IL-4 when activated. In addition, IL-4 is also produced by NK cells [19].

In this study, the serum IL-4 concentration in the SJS/TEN group was higher than that in the EM group (but $p > 0.05$) and the HCs group ($p < 0.05$); was higher in the SJS group than in the TEN group (but $p > 0.05$). In the SJS/TEN group, in the early stage (<6 days after onset), serum IL-4 levels were higher than in the late stage (after 6 days or more of onset) (although $p > 0.05$). The concentration of IL-4 at the time of admission was higher than at the time of re-epithelialization (3.0 vs. 1.1 pg/mL, $p > 0.05$). Serum IL-5 levels did not differ between the SJS/TEN group compared with the EM and HCs groups and between the SJS and TEN groups. At the time of admission, the SJS/TEN group had a serum IL-5 concentration of 4.5 pg/mL; at the time of re-epithelialization, it decreased to 1 pg/mL, and the difference was statistically significant with $p = 0.01$. Thus, when the disease improves, the concentration of IL-5 decreases, but the role of IL-5 in SJS/TEN is not prominent. In contrast, IL-5 plays a key role in eosinophil-mediated inflammation because

it catalyzes differentiation and prolongs the life of these leukocytes [19].

Serum IL-13 levels did not differ between the SJS/TEN and EM groups, between the SJS and TEN groups, between at the time of admission and at the time of re-epithelialization. Our results are different from previous studies. According to Quaglino *et al.*, patients with SJS/TEN had increased serum IL-13 levels while EM patients did not [21].

Thus, in our study, the serum concentration of Th2-derived cytokines (IL-4, IL-5, and IL-13) in the SJS/TEN group was not higher than in the EM group and there was no significant change according to the clinical progression of SJS/TEN. This proves that in SJS/TEN, Th1 may play a more important role than Th2. This statement of ours is also consistent with previous research [22]. The role of Th2 is more evident in other skin diseases such as atopic dermatitis, graft-versus-host disease, and disseminated leishmaniasis. Dupilumab is an effective biologic in the treatment of atopic dermatitis in adults [19]. Its mechanism of action is against the α subunit of the IL-4 receptor, thereby inhibiting IL-4 and IL-13 (which are structurally similar) [19]. In acute asthma in children, serum levels of Th2 cytokines increased, on the contrary, TNF-α levels decreased (compared to healthy children), indicating that children with bronchial asthma increased the inflammatory response in the direction of Th2 cells, decreased response in the Th1 direction.

EM is a cutaneous or mucocutaneous reaction characterized by typical or atypical target lesions. It can be caused by microorganisms (herpes simplex virus, *Mycoplasma pneumoniae*) or by drugs, or possibly both, or idiopathic. In the early stages, SJS may have erythematous rashes, and atypical target lesions, easily confused with EM. Early diagnosis of SJS in the early stages can help early treatment, avoiding serious complications for patients. Caproni *et al.* showed that skin biopsies of SJS/TEN expressed all cytokines TNF-α, IFN-γ, IL-2, IL-5, IL-13, CCR3 (C-C chemokine receptor type 3), CXCR3 (C-X-C motif chemokine receptor 3) and CXCR4 were stronger than EM skin samples. All skin samples of SJS/TEN and EM expressed more potent cytokines than healthy human skin samples. Th1 responses predominantly in EM, in contrast, the imbalance between Th1 and Th2 was not significant in SJS/TEN. TNF-α is strongly expressed in skin lesions of SJS/TEN, which may be related to epidermal necrosis. IFN-γ played an important role in both EM and SJS/TEN. IL-2, IL-5, and IL-13 contribute to the immune-inflammatory mechanism in these diseases. Chemokine receptors are involved in the mobilization of inflammatory cells to skin lesions [23]. The limitation of our study is that it did not biopsy the skin, and did not evaluate the expression of cytokines on the biopsy specimen.

Conclusion

The serum concentrations of Th2-derived cytokines (IL-4, IL-5, and IL-13) were not higher in the SJS/TEN group than in the EM group and there was no significant change in the clinical progression of SJS/TEN, except the serum level of IL-5.

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