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[1]Department of Dermatology and Venereology, Hanoi Medical University, Hanoi, Vietnam
[2]Department of Outpatient, National Hospital of Dermatology and Venereology, Hanoi, Vietnam
[3]Hanoi-Amsterdam Highschool for the Gifted
[4]Department of Health Finance and Health Technology Assessment, Health Strategy and Policy Institute

Corresponding author: Dr. Nguyen Thi Ha Vinh, MD. Ph.D., Hanoi Medical University, Hanoi, Vietnam, 1A Ton That Tung Street, Dong Da, Hanoi, Vietnam. Email: havinhnguyen.derm@gmail.com; ORCID ID: 0000-0001-6066-363X.

Serum Concentrations of IL-18, IL-21, IL-22, IL-23, IL-27, and IL-31 in Patients With Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis and Their Correlation With Disease Severity

Tran Thi Huyen[1,2], Nguyen Hoang Phuc[3], Pham Thi Lan[1,2], Le Huyen My[2], Nguyen Thi Ha Vinh[1,2], Dao Anh Son[4], Le Huu Doanh[1,2]

ABSTRACT

Background: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening conditions marked by extensive epidermal necrolysis and skin sloughing. **Objective:**: The study aimed to assess the serum levels of specific proinflammatory interleukins (IL-18, -21, 22, -23, -27, and -31) and their relationship with the severity of SJS/TEN within the Vietnamese population. **Methods:** This descriptive cross-sectional study was conducted from 2018 to 2020. Serum levels of IL-18, -21, -22, -23, -27, and -31 were measured using the fluorescence covalent microbead immunosorbent assay. **Results**: The study included 61 patients (29 males and 32 females; 21 with SJS and 40 with TEN), with a median age of 51 years (interquartile range: 37-58), and 20 healthy controls. The median lesional area covered 45% of the body surface area (interquartile range: 8-70%). The most frequently identified medications were traditional medicine (19 patients; 31.15%), allopurinol (9 patients; 14.75%), and carbamazepine (8 patients; 13.11%). In the TEN group, the serum level of IL-18 was significantly elevated compared to the healthy control group. A correlation was found between serum levels of IL-18 and IL-27 and the lesional area in SJS/TEN patients, as well as between serum levels of IL-18 and IL-31 and the lesional area in TEN patients. **Conclusion:** Serum levels of IL-18 were increased in TEN group. Additionally, serum concentrations of IL-18, IL-27, and IL-31 were associated with disease severity as indicated by the lesional area. These interleukins may play an important role in the pathogenesis of SJS/TEN.

Keywords: Interleukin-18, interleukin-27, interleukin-31, Steven-Johnson syndrome, toxic epidermal necrolysis.

1. BACKGROUND

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe conditions characterized by extensive skin cell death and shedding (1). The main underlying process of SJS/TEN involves widespread apoptosis and necroptosis of skin cells triggered by drug-induced cytotoxic T lymphocytes (2, 3). Certain medications, like carbamazepine and allopurinol, have been linked to specific human leukocyte antigen (HLA) types, suggesting a need for HLA screening before administering these drugs to reduce SJS/TEN occurrences (1, 4, 5). Despite being rare, SJS/TEN pose significant health risks with mortality rates of 4.8% for SJS and 14.8% for TEN per million people (6-9). Drugs commonly associated with these conditions include allopurinol, carbamazepine, cotrimoxazole, and abacavir (4, 10).

The molecules associated with apoptosis, including tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and inducible nitric oxide (NO), contributed to the drug-induced immune response that resulted in keratinocyte injury (2, 3, 5, 11-13). The apoptosis pathways in keratinocytes emphasized the significance of soluble Fas ligand (FasL), perforin, and gran-

Characteristics	SJS/TEN patients (N = 61)		SJS patients (N = 21)		TEN patients (N = 40)		HCs (N = 20)	
Age, median (IQR)	51	37 - 58	43	32-54	52	38-59.5	49	36 - 55
Gender, n (%)								
Male	29	47.54	9	42.86	20	50	11	55.00
Female	32	52.46	12	57.14	20	50	9	45.00
Diagnosis, n (%)								
SJS	21	34.43	21	100	0	0	NA	NA
TEN	40	65.57	0	0	40	100	NA	NA
Lesional area (% body surface area), median (IQR)	45	8 - 70	7	5-8	60	42.5-90	NA	NA
Causes, n (%)								
Allopurinol	9	14.75	6	28.57	3	7.5	NA	NA
Carbamazepine	8	13.11	5	23.81	3	7.5	NA	NA
Phenylbutazone	1	1.64	1	4.76	0	0	NA	NA
Traditional medicine	19	31.15	2	9.52	17	42.5	NA	NA
Unknown	24	39.34	7	33.33	17	42.5	NA	NA
Fever, n (%)	37	60.66	13	61.90	24	60	NA	NA
Mucosal lesion, n (%)	56	91.80	21	100	35	87.5	NA	NA
Oral mucosal lesion, n (%)	55	90.16	21	100	34	85	NA	NA
Pneumoniae, n (%)	7	11.48	1	4.76	6	15	NA	NA
Liver enzyme increase, n (%)	24	39.34	8	38.10	16	40	NA	NA
Kidney injury, n (%)	19	31.15	7	33.33	12	30	NA	NA
SCORTEN, median (IQR)	2	1 - 2	1	0-2	2	1-2	NA	NA
White blood count, n (%)								
Increase	12	19.67	6	28.57	6	15	NA	NA
Remain	46	75.41	14	66.67	32	80	NA	NA
Decrease	3	4.92	1	4.76	2	5	NA	NA

Table 1. General characteristics of SJS/TEN patients and HCs. IQR, interquartile range; SCORTEN, severity-of-illness score for toxic epidermal necrolysis; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; NA, not applicable

zyme B. Elevated levels of T helper 1 (Th1) cytokines were found in both the affected skin and peripheral blood of patients with SJS/TEN (1, 2, 4, 14). Assessing serum cytokines could have enhanced the ability to monitor and predict the severity of the disease. In this research, the serum concentrations of various proinflammatory cytokines (IL-18, -21, -22, -23, -27, and -31) and their relationship to the severity of SJS/TEN in the Vietnamese population were examined.

2. OBJECTIVE

The study aimed to assess the serum levels of specific proinflammatory interleukins (IL-18, -21, 22, -23, -27, and -31) and their relationship with the severity of SJS/TEN within the Vietnamese population

3. PATIENTS AND METHODS

Sixty-one patients diagnosed with SJS/TEN were included in this research. Eligibility required participants to be at least 17 years of age and hospitalized within 10 days of symptom onset, specifically marked by the initial appearance of mucocutaneous or eye-related lesions. Individuals were excluded from the study if they tested positive for HIV, experienced multi-organ failure, or had sepsis. To serve as a comparison group, 20 healthy controls (HCs) were also recruited. Patient assessments included monitoring vital signs, evaluating systemic symptoms, and calculating the extent of skin detachment as a percentage of total body surface area. SJS and TEN were defined using the Bastuji-Garin criteria, which distinguishes them by the extent of epidermal detachment: i) SJS involves less than 10%, ii) TEN affects more than 30%, and iii) overlapping SJS/TEN cases cover between 10% and 30% (9).

Study Design

This research utilized a cross-sectional descriptive approach, conducted at the National Hospital of Dermatology and Venereology located in Hanoi, Vietnam, over the period between 2018 and 2020.

Ethical Clearance

Ethical approval for the study was granted by the Ethical Review Committee on Research Involving Human Subjects at Hanoi Medical University (Approval number: 04NCS17, issued on February 8, 2018). All participants provided written informed consent prior to their involvement in the study.

Analysis of Cytokines

For a group of 61 patients with SJS/TEN, 3-5 ml of blood was drawn before initiating treatment. The collected blood was left to clot at room temperature for a duration of 10-20 minutes, followed by centrifugation for 20 minutes at a speed of 2000-3000 r.p.m. The resulting serum was separated and stored at -80°C until cytokine levels were assessed. Concentrations of IL-18, -21, -22, -23, -27, and -31 in the serum were quantified using the fluorescence covalent microbead immunoassay (FCMIA) with the ProcartaPlex Immunoassay Panels kit (Thermo Fisher Scientific, USA; Lot numbers: IL-18, 310964-003; IL-21, 329506-001; IL-22, 234274-006; IL-23, 306605-001; IL-27, 383720-001; IL-31, 373984-003).

Statistical Analysis

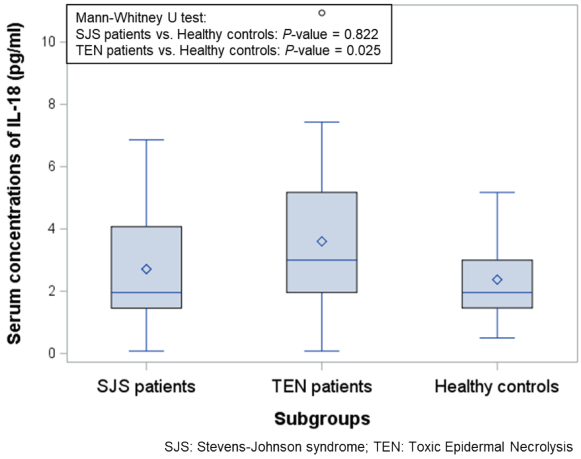
Cytokines (pg/ml)	HCs (N = 20)		SJS/TEN patients (N = 61)		*P*-value[1]	SJS patients (N = 21)		*P*-value[2]	TEN patients (N = 40)		*P*-value[3]
	Median	IQR	Median	IQR		Median	IQR		Median	IQR	
IL-18	1.96	1.46-3	3.00	1.96-4.07	0.097	1.96	1.45-4.07	0.822	3.00	1.96-5.17	0.025
IL-21	0.75	0.75-0.75	0.75	0.75-0.75	1.000	0.75	0.75-0.75	1.000	0.75	0.75-0.75	1.000
IL-22	5.16	5.04-5.35	5.29	5.1-5.48	0.223	5.29	5.16-5.54	0.152	5.26	5.1-5.45	0.380
IL-23	0.04	0.04-0.04	0.04	0.04-0.04	0.394	0.04	0.04-0.04	0.152	0.04	0.04-0.04	0.707
IL-27	0.57	0.57-0.57	0.57	0.57-0.57	0.194	0.57	0.57-0.57	1.000	0.57	0.57-0.57	0.105
IL-31	0.14	0.14-0.14	0.14	0.14-0.29	0.356	0.14	0.14-0.29	0.422	0.14	0.14-0.63	0.389

Table 2. Comparisons in serum concentrations of cytokines between the SJS/TEN patients and HCs. IL, interleukin; IQR, interquartile range; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis, [1]Mann-Whitney U test between SJS/TEN patients and HCs [2]Mann-Whitney U test between SJS patients and HCs [3]Mann-Whitney U test between TEN patients and HCs

The data were reviewed and cleaned before entry. Data entry and processing were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical analyses were conducted with appropriate tests: the Mann-Whitney U test compared mean and/or median values between groups, while the Spearman rank correlation test assessed correlations. Statistical significance was defined as a P-value <0.05.

4. RESULTS

A total of 61 participants, including 29 males and 32 females, were recruited for this study. Of these, 21 had SJS and 40 had TEN. The median age was 51 years (interquartile range: 37-58). The median percentage of body surface area affected was 45% (interquartile range: 8-70%). The drugs most commonly associated with the condition were traditional medicine in 19 patients (31.15%), allopurinol in 9 patients (14.75%), and carbamazepine in 8 patients (13.11%). A full overview of the clinical and laboratory characteristics is provided in Table 1. Table 2 and Figure 1 display the median serum concentrations and interquartile ranges of interleukins IL-18, -21, -22, -23, -27, and -31 across the HCs group, SJS/TEN group, SJS group, and TEN group, along with the associated statistical analysis. In the TEN group, the serum concentration of IL-18 was significantly higher compared to the HCs group. However, there were no statistically significant differences in the serum levels of IL-18, -21, -22, -23, -27, and -31 between patients with SJS and those with TEN. A correlation was observed



SJS: Stevens-Johnson syndrome; TEN: Toxic Epidermal Necrolysis

Figure 1. Comparison in serum concentrations of IL-18 between SJS/TEN patients and healthy controls

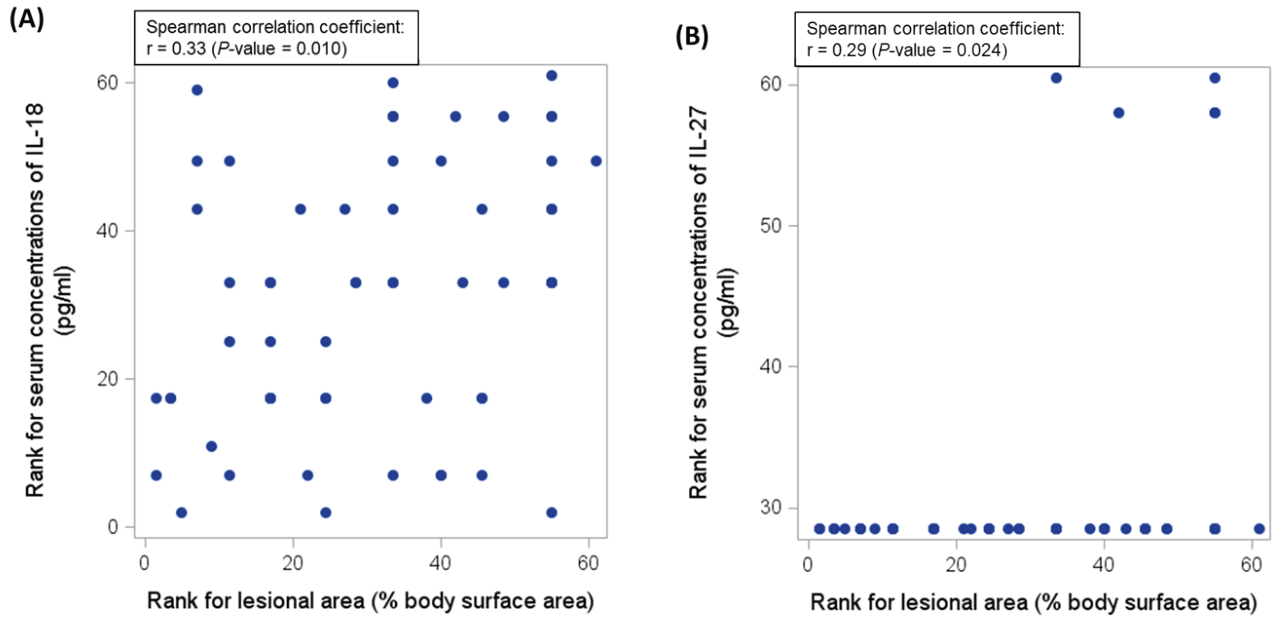


Figure 2. Correlations between lesional area and (A) serum concentrations of IL-18, and (B) serum concentrations of IL-27 in SJS/TEN patients.

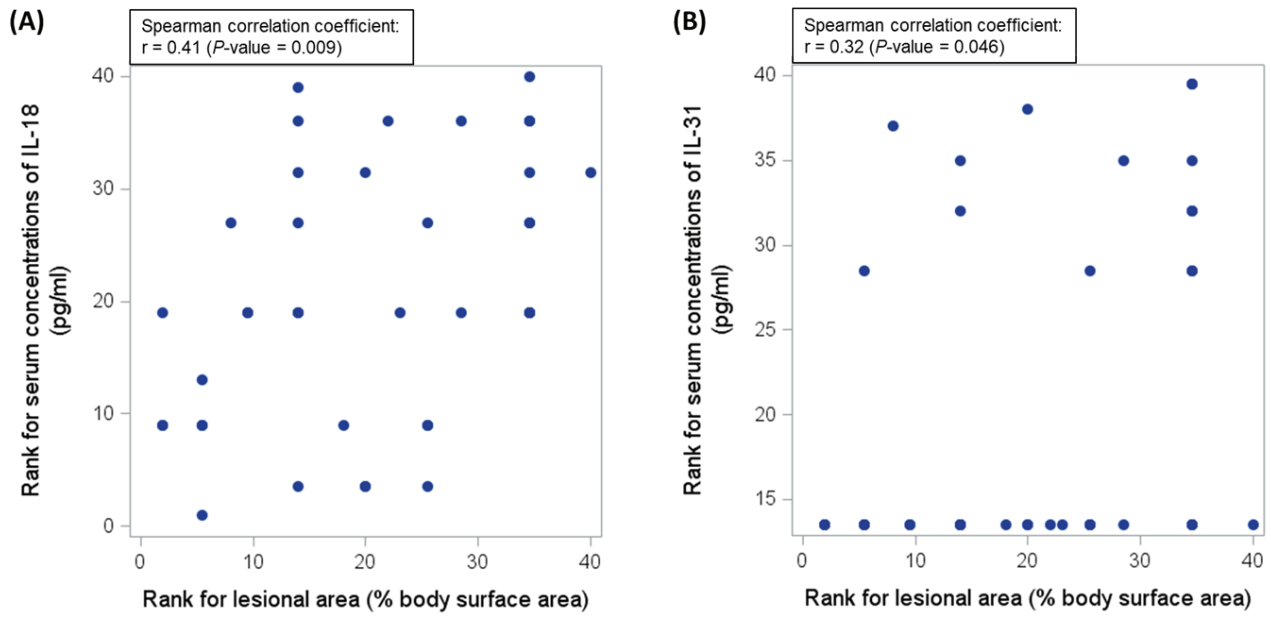


Figure 3. Correlations between lesional area and (A) serum concentrations of IL-18, and (B) serum concentrations of IL-31 in TEN patients.

between the serum levels of IL-18 and IL-27 and the affected body surface area in patients with SJS/TEN (Figure 2). In TEN patients, serum IL-18 and IL-31 concentrations were also correlated with the lesional area (Figure 3).

5. DISCUSSION

Keratinocyte death is a hallmark characteristic of SJS/TEN. Apoptosis of keratinocytes has been linked to cytokines involved in apoptotic pathways, including TNF-α, sFasL, granulysin, sTRAIL, and IFN-γ. These cytokines were found to be elevated, although with variation, especially during the initial phase of SJS/TEN, and demonstrated distinct patterns as the condition progressed. Both serum and blister fluid showed increased concentrations of these cytokines compared to controls, with blister fluid levels being higher than those in the serum. Interestingly, while sTRAIL, IFN-γ, and TNF-α levels remained fairly consistent, sFasL and granulysin levels declined sharply over time. Early in the disease, CD8+ Tcells and natural killer (NK) cells were dominant in the blister fluid, but their prevalence decreased as CD14+ cell percentages grew (13).

Caproni presented additional proof demonstrating that TNF-α was highly elevated in SJS/TEN lesions, implying its involvement in the epidermal necrosis seen in these conditions (15). Additionally, IFN-γ was identified as a key factor in both erythema multiforme (EM) and SJS/TEN (6). Moreover, IL-2, -5, and -13 were recognized as contributors to the immune-driven skin inflammation associated with these diseases. Chemokine receptors were thought to play a role in attracting inflammatory cells to the affected areas. EM showed a clear Th1 polarization, while SJS/TEN lesions exhibited a combination of Th1/Th2 pattern (16). In this investigation, serum IL-18 levels were notably elevated in the TEN group compared to HCs. There were no significant differences in serum levels of IL-18, -21, -22, -23, -27, and -31 between SJS and TEN patients. However, links were observed between serum IL-18 and IL-27 concentrations and the extent of skin lesions in SJS/TEN patients, as well as between serum IL-18 and IL-31 levels and the lesion size in TEN patients.

The underlying mechanisms behind SJS/TEN remain poorly understood, and definitive treatments have yet to be established. The involvement of the innate immune system, particularly monocytes, neutrophils, and T cells, suggests a more intricate pathophysiology (17). Further research into the development of SJS/TEN is likely to result in advancements in both diagnosis and treatment options. CD8+ Tcells play a central role in the progression of SJS/TEN. In addition to the primary cytotoxic protein granulysin, other cytotoxic agents, including Fas, Fas ligand (FasL), perforin, and granzyme B, were also involved in SJS/TEN pathogenesis. This suggests that drug-specific CD8+ cytotoxic T cells triggered keratinocyte apoptosis via perforin and granzyme B, and the apoptotic response was further amplified through FasL-Fas interactions. In serum cytokine analysis, patients with SJS/TEN showed higher levels of tumor necrosis factor-α, IL-6, -18, -15, and -12p70 when compared to healthy individuals (18, 19).

Interleukin-18, part of the IL-1 cytokine family, is recognized for enhancing the activity of the innate immune system. It activates both innate and adaptive immune responses by targeting Th1 cells, macrophages, NK cells, natural killer T (NKT) cells, B cells, dendritic cells (DCs), and unpolarized T cells to produce interferon-gamma (IFN-γ) when IL-12 is present. In the absence of IL-12, IL-18, together with IL-2, triggers the release of Th2 cytokines from NK cells, CD4+ NKT cells, and differentiated Th1 cells. Moreover, IL-18, in conjunction with IL-3, activates basophils and mast cells to secrete IL-4 and IL-13. IL-18 exhibits a wide range of effects

depending on the surrounding cytokines, highlighting its important role in both health and disease conditions (19).

Interleukin-27, on the other hand, is acknowledged for its diverse impact on immune regulation. Initially thought to be involved mainly in the development of Th1 responses, IL-27 has now been identified as a strong inhibitor of various inflammatory processes by modulating the functions of CD4+ and CD8+ T cells, inducing IL-10, and fostering specific T regulatory cell responses. This aspect of IL-27's function has shed light on its role in controlling immune hyperactivity during infectious and autoimmune inflammation. Despite its inhibitory role, IL-27's ability to stimulate CD8+ T cells has been notable in vaccine and cancer studies. Its involvement in antibody-mediated conditions has also drawn attention to its effects on innate immunity and humoral responses across different diseases. Ongoing research aims to apply findings from experimental models to human health and explore IL-27 as a potential therapeutic target (20).

Interleukin-31 (IL-31) has been linked to multiple atopic conditions, including atopic dermatitis (AD), allergic rhinitis, and increased airway reactivity, and is recognized as a key factor driving itchiness in AD. In AD, Th2 cells, which are essential to its pathogenesis, secrete high quantities of Th2-related cytokines, among which IL-31 is significant. This cytokine facilitates inflammatory responses, triggers immune regulatory pathways, and promotes both itch sensation and neuronal growth by activating the receptor complex formed by IL-31 receptor A (IL31RA) and Oncostatin M receptor (OSMRβ). IL31RA is found in dorsal root ganglia neurons of both humans and mice, as well as in epithelial cells like keratinocytes and various innate immune cells. IL-31 is vital for the communication between the nervous and immune systems, especially in AD and associated pruritus, as evidenced by recent clinical trials involving an anti-IL-31 antibody (15,16).

This research had several limitations. Serum samples were collected several days after the onset of SJS/TEN, which may have led to decreased cytokine levels. Some patients had also received systemic corticosteroids prior to hospitalization. Cytokine concentrations were assessed only in serum, without measurements from blister fluid or skin tissue. Elevated levels of Fas, Fas ligand, IL-8, and B-cell lymphoma (Bcl)-2 were found in SJS/TEN blister fluid and skin tissue compared to healthy controls. Additionally, IL-2, IL-6, TNF-α, TRAIL, IFN-γ, and matrix metalloproteinase-2 were higher in SJS/TEN blister fluid than in lesional controls. Granulysin, IL-33, TGF-beta-1, and IL-13 levels were increased in SJS/TEN skin tissue compared to lichen planus tissue, and IL-13, IFN-γ, IL-2, and IL-5 were elevated compared to epidermal necrolysis tissue (15). Overall, a variety of cytokines and cytotoxic proteins were present at higher levels in the blister fluid and skin tissue of SJS/TEN patients. These proteins could be pathogenic and serve as potential biomarkers for diagnosis, disease severity, and progression, as well as therapeutic targets.

6. CONCLUSION

Serum concentrations of IL-18 were elevated in patients with TEN. Additionally, serum levels of IL-18, IL-27, and IL-31 correlated with disease severity, as indicated by the lesional area. These interleukins may play an important role in the pathogenesis of SJS/TEN.

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