Serum interleukin-21 level in patients with severe adverse cutaneous drug reactions and correlation with disease severity

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Introduction
Interleukin-21 (IL-21) is accepted to play a pathogenic part in development of unfavorable cutaneous medicate responses. Adverse cutaneous drug reactions create a wide run of clinical signs such as pruritus, maculopapular ejections, urticaria, angioedema, fixed drug eruption, erythema multiforme, vesiculobullous responses (e.g. Stevens–Johnson syndrome and toxic epidermal necrolysis), and exfoliative dermatitis.

Patients and methods
Twenty patients (drug-eruption group) and 14 healthy controls (control group) were recruited from Assiut University Hospitals' Dermatology Department and Outpatient Clinic. Data were collected in the period from October 2017 to December 2018. Patients were assessed clinically by percentage of surface area of the body involvement (body surface area %) and score of toxic epidermal necrolysis. At presentation and after 1 month of treatment, blood samples were taken to evaluate serum IL-21 levels using an enzyme-linked immunosorbent assay.

Results
Inside the study, the cruel serum IL-21 level was considerably greater than in the control group, in drug-eruption group was 575.58 ± 94.67 ng/dl, and in the control group was 128.00 ± 73.94 ng/dl with *P* value of 0.000. The drug-eruption group had a significantly higher serum level of IL-21 before treatment than after treatment with *P* value of 0.000. Additionally, there was a critical relationship between IL-21 levels in the blood and the severity of the condition. Before and after therapy, there was a significant positive association between blood IL-21 levels and the proportion of body surface area involvement.

Conclusion
IL-21 levels in the blood were significantly higher in EM and SJS/TEN patients, suggesting that it may have a role in the etiology of EM and SJS/TEN and it could be employed as a marker for the severity of SJS/TEN and patient prognosis in the future.

Keywords:
erythema multiforme, Steven–Johnson syndrome and interleukin-21, toxic epidermal necrolysis

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Introduction

Unfavorable cutaneous medicate responses are undesirable and often unexpected side effects that occur, regardless of a medication's intended therapeutic aim [1].

Erythema multiforme is an acute immune-mediated, intense, self-limiting, recurrent mucocutaneous disorder that manifestation with a reaction pattern as a consequence of allergic host response to antigenic challenge. It is a mild-spread hypersensitivity reaction caused by T cells with cytotoxic properties in the epithelium that induces apoptosis in keratinocytes, leading to cell necrosis [2].

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are unprecedented, intense, and possibly life-threatening unfavorable cutaneous sedate responses. They appear as scalded skin as a result of significant keratinocyte death, which causes the dermal–epidermal junction to separate, resulting in the separation of sections of skin [3–7].

SJS is defined as an epidermal loss of less than 10% of the body surface area (BSA), while TEN is defined as a loss of more than 30% of the BSA. The SJS–TEN overlap refers to the spectrum of epidermal loss between 10 and 30% [6].

Interleukin-21 (IL-21) is the newest member of a group of cytokines whose receptors all share the same cytokine receptor γ chain [8]. Although lymphoid cells produce IL-21, it is highly expressed on a variety of immune and nonimmune cells (native and

activated T cells, B cells, NK cells, dendritic cells, and macrophages) (keratinocytes and endothelial cells). Subsequently, Tfh cells, Th17 cells, and regulatory T cells have all been identified to be major providers of IL-21 [3,9–12].

In recent years, a recently discovered CD4+ T-cell subset known as peripheral helper T cells has been revealed to produce IL-21. Peripheral helper T cells are primarily seen in inflammatory areas and are known to express IL-21 [13,14].

IL-21 controls both the innate and adaptive immune responses, and it is not only involved in antitumor and antiviral responses, but it also plays a role in the development of autoimmune illnesses and inflammatory disorders [15].

B cells' proliferation and survival, as well as their differentiation into immunoglobulin-producing cells, are all aided by IL-21 [8,16]. IL-21 works in concert with IL-15 or IL-7 to promote the proliferation of both naive and memory CD8+ T cells [17]. The cells' proliferative response to IL-21 in the absence of TCR signals suggests that IL-21 plays a function in innate immune responses. CD8+ T-cell growth can be induced by IL-21 [8,16]. IL-21 acts synergistically with IL-15 or IL-7 to induce proliferation of both naive and memory phenotype $CD8^+$ T cells [17]. The proliferative response of these cells to IL-21 in the absence of TCR signals implies a role for IL-21 in innate immune responses. IL-21 can induce $CD8^+$ T-cell expansion [18].

IL-21 is a cytokine with powerful regulatory effects on immune-system cells (NK cells and T cells) that can kill virally infected cells [19].

IL-21R, a class-I cytokine heterodimeric receptor, has a common cytokine-receptor chain with other cytokine families, including IL-2, IL-4, IL-7, IL-9, and IL-15, as a receptor for IL-21. IL-21R is mostly found on lymphoid cells such as thymocytes, splenocytes, and lymph-node cells [20].

The goal of this study was to quantify and compare serum IL-21 levels in patients who had cutaneous medication responses (erythema multiforme, SJS, and TEN).

Aim

(1) To compare the levels of serum IL-21 in patients with severe adverse cutaneous drug reactions and healthy controls.
(2) To compare the levels of serum IL-21 in patients with severe adverse cutaneous drug reactions (SJS and TEN) to those with a lesser form (EM).
(3) To compare serum IL-21 levels before and after therapy in individuals with severe adverse cutaneous drug reactions, and to see if there is a link between disease severity and serum IL-21 levels.

Patients and methods

We enrolled 20 patients who were presented with adverse cutaneous drug eruption (drug-eruption group). Fourteen people served as controls in the study (control group).

Site of the study: they were chosen from Assiut University Hospital's outpatient dermatological clinic and the Department of Dermatology, Venereology, and Andrology.

Duration of the study: data were collected in the period from October 2017 to December 2018.

(1) Inclusion criteria:
    (a) Patients with definite drug history were considered for the study.
    (b) Age range: 15–60 years.

Exclusion criteria:
(1) Patients who had received topical or systemic medication (corticosteroids, intralesional steroid injection, and immunosuppressive therapy) within the previous 4 weeks prior to the trial.
(2) Patients who started phototherapy within 6 months of the study's start date.
(3) Patients who have had diabetes, anemia, thyroid abnormalities, chronic liver or renal illness, atopy, or parathyroid disorders in the past.
(4) Patients who have been diagnosed with cancer or autoimmune illnesses.
(5) Women who are pregnant or nursing.

Approach to the patient

Calculating the surface area of skin detachment was used to determine the extent of each patient's skin lesions in which peeling took place of necrotic epidermis in sheets, leaving a scalded appearance [21]. The Wallace rule of nines is a technique for estimating the impacted total BSA [22].

Patients with SJS (1–10%), SJS/TEN (11–30%), or TEN (>30%) were categorized [23].

The SCORe of Toxic Epidermal Necrosis scale was used to assess the SJS/TEN group, in which The SCORe of Toxic Epidermal Necrosis scale varied from 0 (no factor present) to 7 (every factor present)

(all factors present) [24]. Age more than 40 years, malignancy, tachycardia more than 120 beats/min, percentage of epidermal detachment more than 10%, serum urea more than 10 mmol/l, serum glucose level more than 14 mmol/l, and serum bicarbonate 20 mmol/l are all factors to consider [25].

Within 1 week of the commencement of the skin eruption, the first blood samples were taken from the patients.

Ethical consideration

The Assiut Faculty of Medicine's Ethical Committee approved the study. Our study was registered at ClinicalTrials.gov Identifier: NCT03166241. All data was kept private and confidential. Each participant was told of the study's purpose and gave their informed oral permission.

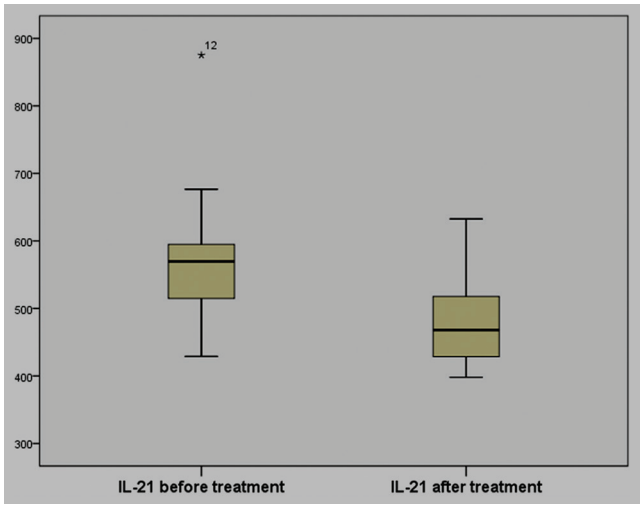
Results

The cruel age of the patients was 43.90 ± 14.48. Twenty percent of the patients were male and 80% were female. In the drug-eruption group, the mean serum IL-21 level was considerably greater, in drug-eruption group was 575.58 ± 94.67 ng/dl, and in the control group was 128.00 ± 73.94 ng/dl with *P* value of 0.000 (Table 1, Fig. 1).

The drug-eruption group had significantly greater serum levels of IL-21 before treatment than after treatment (*P* = 0.000) (Table 2, Fig. 2).

There was no discernible link between IL-21 levels in the blood before and after treatment and the patients' age (Tables 3, 4).

Figure 1



The levels of IL-21 in the blood of the studied groups. IL-21, interleukin-21.

There was a significant relationship between blood IL-21 levels before therapy and the severity of the illness, with serum IL-21 levels being higher in the SJS/TEN group than in the erythema multiforme group (*P* = 0.001) (Table 5).

Table 1 Interleukin-21 levels in the blood of the studied groups before treatment

IL-21	Patients (*n*=20)	Control (*n*=14)	*P*
Mean±SD	575.58±94.67 ng/dl	128.00±73.94 ng/dl	0.000*
Median (range)	569.8 (429.0-875.0) ng/dl	108.5 (41.5-266.5) ng/dl	

IL-21, interleukin-21. *Statistically significant difference (*P*< 0.05).

Table 2 Interleukin-21 levels in the blood in patients' group before and after treatment

IL-21	Before treatment (*n*=20)	After treatment (*n*=20)	*P*
Mean±SD	575.58±94.67 ng/dl	480.48±65.83 ng/dl	0.000*
Median (range)	569.8 (429.0-875.0) ng/dl	468.0 (398.0-632.5) ng/dl	

IL-21, interleukin-21. *Statistically significant difference (*P*< 0.05).

Table 3 Interleukin-21 levels in the blood before treatment in relation to age of the patients

	IL-21 before treatment		*P*
	Mean±SD	Median (range)	
Age (years)			
<30	508.67±11.68	511.0 (496.0-519.0)	0.064
≥30	587.38±98.17	582.0 (429.0-875.0)	

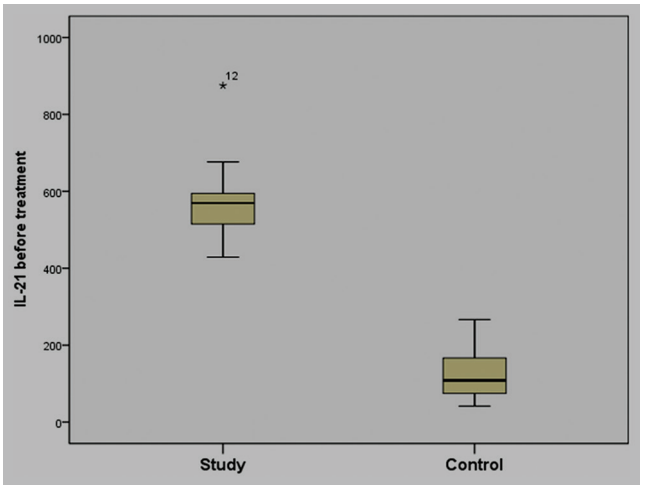
IL-21, interleukin-21.

Table 4 The age of the patients and the serum level of interleukin-21 following treatment

	IL-21 after treatment		*P*
	Mean±SD	Median (range)	
Age (years)			
<30	428.00±8.54	427.0 (420.0-437.0)	0.090
≥30	489.74±67.30	483.0 (398.0-632.5)	

IL-21, interleukin-21.

Figure 2



Levels of IL-21 in the blood before and after treatment in patients. IL-21, interleukin-21.

There was also a significant relationship between IL-21 serum levels following treatment and illness severity ($P = 0.006$) (Table 6).

Before treatment, there was a significant positive association between serum IL-21 levels and the percentage of BSA participation ($P = 0.000$), as well as the TEN score ($P = 0.030$) (Table 7).

Moreover, critical positive relationship was found between serum IL-21 level after treatment and the rate of BSA association ($P = 0.000$), and score of TEN ($P = 0.000$) (Table 8).

Conclusion

IL-21 is one of the ILs, which has a cytotoxic destructive effect on keratinocytes and their apoptosis with epidermal necrosis. Its serum level was investigated in individuals with potentially fatal cutaneous drug responses (SJS and TEN) with comparison to their minor form (EM), healthy controls, and before and after treatment. Also, the results were correlated with disease severity.

Our findings revealed that blood levels of IL-21 were higher in both the EM and SJS/TEN groups compared with healthy controls, and that IL-21 levels correlated favorably with disease-severity indicators. After 1 month of corticosteroid treatment, the serum level of IL-21 in the patients' group also reduced.

Also, in the study done by Morsy *et al*. [26], in EM and SJS/TEN, patients showed significant higher serum level of IL-17 in the EM-minor group compared with the HC group and serum IL-17 levels in SJS/TEN group were significantly higher than those of both the EM-minor and HC groups, which also showed that increased serum IL-17 levels were also associated with greater TBSA and with mucous membrane involvement.

From the previous findings, we concluded that:

(1) IL-21 levels in the blood were significantly higher in EM and SJS/TEN patients, suggesting that it may have a role in the etiology of EM and SJS/TEN.
(2) The severity of EM and SJS/TEN medication reactions may be influenced by IL-21 levels in the blood. The results of this study suggest that serum IL-21 could be employed as a marker for the severity of SJS/TEN and patient prognosis in the future.

Table 5 The severity of the problem according to clinical diagnosis and the serum level of interleukin-21 before therapy

Diagnosis	IL-21 before treatment		*P*
	Mean±SD	Median (range)	
SJS/TEN	625.79±88.86	587.5 (551.0-875.0)	
EM major	518.40±14.10	519.0 (500.0-537.5)	0.001*
EM minor	470.00±35.93	485.0 (429.0-496.0)	

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis. *Statistically significant difference ($P< 0.05$).

Table 6 The severity of the problem according to clinical diagnosis and the serum level of interleukin-21 before therapy

	IL-21 after treatment		*P*
	Mean±SD	Median (range)	
SJS/TEN	513.17±62.04	492.5 (430.5-632.5)	
EM major	445.10±35.13	437.0 (420.0-506.5)	0.006*
EM minor	408.67±15.95	401.0 (398.0-427.0)	

IL-21, interleukin-21; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis. *Statistically significant difference ($P< 0.05$).

Table 7 Correlation of interleukin-21 before treatment with body surface area % and score of toxic epidermal necrolysis

	IL-21 before treatment	
	r	*P*
BSA%	0.961	0.000*
Score of TEN	0.626	0.030*

BSA, body surface area; IL-21, interleukin-21; TEN, toxic epidermal necrolysis. *Statistically significant difference ($P< 0.05$).

Table 8 Correlation of interleukin-21 after treatment with body surface area % and score of toxic epidermal necrolysis

	IL-21 after treatment	
	r	*P*
BSA%	0.877	0.000*
Score of TEN	0.906	0.000*

BSA, body surface area; IL-21, interleukin-21; TEN, toxic epidermal necrolysis. *Statistically significant difference ($P< 0.05$).

Recommendations

(1) Future studies are needed with a higher number of patients to determine the role of the IL-21 cytokine in cases of drug eruption.
(2) Interrupting the IL-21 signaling pathway as a therapeutic strategy for the treatment of inflammatory, allergy, and immunologic illnesses warrants further research.

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Conflicts of interest

There are no conflicts of interest.

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