ORIGINAL ARTICLE

Relationship between serum interleukin-21 and disease severity in patients with psoriasis

Hussein Mohamed Hassab-El-Naby,[1] MD, Ahmed Rashad Elshahed,[1] MD
Maha Mamdouh Abd ELRaheem,[1] MD, Nabil Fathy Esmail,[2] MD

[1]Department of Dermatology, Venereology and Andrology faculty of Medicine-Al Azhar University, *Egypt*
[2]Department of Clinical Pathology Faculty of Medicine-Al Azhar University, *Egypt*

ABSTRACT

Background: Psoriasis is a common, chronic cutaneous disorder with a high relapse rate. Current evidence suggests that psoriasis is a complex immune mediated inflammatory multi-factorial skin disease with a complex pathogenesis. IL-21 has an important role in the control of the growth, survival, differentiation and function of both T and B cells, and excessive production of IL-21 has been associated with the development of multiple immune-mediated diseases. IL-21 could play an important role in the production of pathogenic autoantibodies and end-organ damage in multiple immune-mediated diseases.

Objective: The aim of this work was to estimate the serum level of IL-21 in psoriatic patients in comparison to normal controls and to detect any correlation between serum IL-21 level and severity of the disease.

Subjects and Methods: This study included 40 patients with psoriasis and 25 healthy volunteers as controls. All patients and controls were subjected to full history taking, clinical examination (general and dermatological), severity of psoriasis was assesed by PASI score. Blood sample was collected for determination of serum IL-21 level by ELISA from patients and controls.

Results: The results of this study revealed that the serum level of IL-21 in psoriatic patients was significantly higher than control group and there was a significant positive correlation between serum level of IL-21 and severity of the disease which was evaluated by PASI score.

Conclusion: Serum level of IL-21 was increased in psoriatic patients in comparison to normal controls. IL-21 was positively correlated with severity of the disease evaluated by PASI score. IL-21 may play a major role in the pathogenesis and development of psoriasis and could be used as a marker for disease severity.

KEYWORDS: IL21, psoriasis, PASI

INTRODUCTION

Psoriasis is a common, chronic cutaneous disorder with a high relapse rate. Current evidence suggests that psoriasis is a complex immune mediated inflammatory disease driven primarily by T cells, particularly Th1 and Th17 cells.[1] Psoriasis is a multi-factorial skin disease with a complex pathogenesis. Various predisposing factors have been suggested to play a key role in the pathogenesis as genetic factors and some triggers.[2] *In vitro* studies have revealed a complex interaction of dendritic cells, epidermal keratinocytes, and infiltrated immune cells and their proinflammatory cytokines.[3]

The shift toward T cells in pathogenesis of psoriasis caused by the therapeutic success observed in psoriatic patients with medications that inhibit T-cell functions, such as cyclospo-

Correspondence: *Dr. Ahmed Rashad Elshahid, Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Al-zhar University Cairo, Egypt. Mobile: 002 01006262271. Email: ahmedandro@yahoo.com*

rine A, a substance that diminishes T-cell proliferation and cytokine production transforming the old perception of psoriasis as a localized autoimmune skin disease, to the new perspective of psoriasis as a systemic inflammatory disease with autoinflammatory features and severe associated comorbid conditions. This inflammation is mediated by a link between innate and adaptive immune systems by the dendritic cells.[1] Dendritic cells produce the messenger substances like tumor necrosis factor alpha and interleukin 23 which in turn promote the development of T helper (Th1 and Th17) cells. These T cells secrete mediators that contribute to the vascular and epidermal changes of psoriasis.[4]

IL-21 has an important role in the control of the growth, survival, differentiation and function of both T and B cells and excessive production of IL-21 has been associated with the development of multiple immune-mediated diseases.[5] IL-21 could play an important role in the production of pathogenic autoantibodies and end-organ damage in multiple immune-mediated diseases.[6] The proliferative effect of IL-21 is dependent on STAT1 and STAT3 activation.[7] IL-21 acts in concert with other common γ-chain-dependent cytokines to enhance the growth of CD4+ T cells.[8] Many studies revealed that interleukin -21 might be involved in the epidermal hyperplasia of psoriasis, and its high expression in psoriatic plaques may be related to the pathogenesis of psoriasis.[9]

The aim of this work was to estimate the serum level of IL-21 in psoriatic patients in comparison to normal controls and to detect any correlation between serum IL-21 level and severity of the disease.

SUBJECTS AND METHODS

This study was carried out on 40 patients with psoriasis and 25 healthy volunteers as controls. The patients were selected from the outpatient Dermatology and Venereology clinic of Al-Azhar University hospitals.

Inclusion criteria: Psoriatic patients were either newly diagnosed or washed out from systemic treatment for at least four weeks prior to blood sample collection.

Exclusion criteria: Psoriatic patients who had other autoimmune or systemic disease as inflammatory bowel disease, atopic dermatitis, systemic lupus erythematosus, diabetes, systemic sclerosis or rheumatoid arthritis.

Ethical considaration: All subjects were informed about the aim of the study and an informed consent was signed by each one of them. Permission was obtained from the ethical committee of the faculty of medicine, Al-Azhar University.

Methods

1- Detailed history taking from all patients includes:

a. Personal history:

Name, age, sex, marital status, address and occupation.

b. Present history:

a) Onset, course, duration of the disease.

b) Exacerbating and relieving factors.

c) Previous treatment and the date of stoppage of the last treatment.

c. Family history of psoriasis.

d. Past history of other skin, systemic and auto-immune diseases.

2- Clinical examination for all patients:

a. General examination:

Careful general examination and search for

clinical manifestations suggestive of any systemic disease.

b. Dermatological examination to determine:

a. Site of skin involvement.
b. Distribution of the lesions localized or generalized.
c. Type of psoriasis (plaque, guttate,pustular, nail or palmoplantar).
d. Assessment of severity of psoriasis ac cording to PASI score

PASI score: PASI score was done for all patients according to Kreft et al,[10] as an indication of degree of severity.

3- Blood samples collection from all patients and controls: Blood sample collection for determination of serum IL-21 level by ELISA.

4- Statistical analysis:

Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation and chi-square test by SPSS Version 17.

Mean value $(\bar{X})$: The sum of all observations divided by the number of observation.

$$(\bar{X}) = \frac{\Sigma x}{n}$$

Where Σ = sum & n = number of observations.

Standard Deviation [SD]: It measures the degree of scatter of individual varieties around their mean

$$SD = \sqrt{\frac{\Sigma |x - x|^{-2}}{n-1}}$$

3-Analysis of variance (ANOVA)

ANOVA is a collection of statistical models used in order to analyze the differences between group means and their associated procedures. In its simplest form, ANOVA provides a statistical test of whether or not the means of several groups are equal.

The hypotheses are:

H0: μ1=μ2=μ3

H1: μ1≠μ2≠μ3

The F-test is used for comparing the factors of the total deviation. For example, in one-way or single-factor ANOVA, statistical significance is tested for by comparing the F test statistic

$$F = \frac{\text{variance between treatments}}{\text{variance within treatments}}$$

$$F = \frac{MS_{\text{Treatments}}}{MS_{\text{Error}}} = \frac{SS_{\text{Treatments}}/(I-1)}{SS_{\text{Error}}/(n_T - I)}$$

where MS is mean square, I = number of treatments and n_T = total number of casesto the F-distribution with $I - 1$, $n_T - I$ degrees of freedom.

4-Linear Correlation Coefficient [r]:

$$r = \frac{\Sigma (X-\bar{X})(y-\bar{y})}{\sqrt{\{\Sigma(X-\bar{x})2\}\{\Sigma(y-\bar{y})2\}}}$$

Where:

X= Independent variable.

Y= Dependent variable.

RESULTS

Our patients were divided according to PASI score calculation into 11 patients with mild psoriasis (PASI score 2-11), 17 patients with moderate psoriasis (PASI score16-22), and 12 patients with severe psoriasis (PASI score 26-40). The results of this study revealed that the serum level of IL-21 in psoriatic patients was significantly higher than control group and there was a significant positive correlation between serum level of IL-21 and severity of the disease which was evaluated by PASI score (Tables 1-4 and Fig. 1).

Table 1 Severity of psoriasis according to PASI Score

PASI score		**Range**	2-40
		Mean ± SD	12.95 ± 10.140
	Mild N=11	**Range**	2-11
		Mean ± SD	5.45±2.42
	Moderate N=17	**Range**	16-22
		Mean ± SD	17.76±6.17
	Severe N=12	**Range**	26-40
		Mean ± SD	34.33±3.39

The patients in this study were divided into mild, moderate and severe according to severity of psoriasis which evaluated by PASI score.

Table 2 Comparison between psoriatic patients & control group in relation to Serum level of Interleukin-21

	IL-21(pg/ml)	
	Patients	**Control**
Range	57-311.9	25-50
Mean	114.92	34.84
+SD	58.89	11.41
t. test	**6.702**	
p. value	**0.000***	

The serum level of IL-21was statistically significant higher in patients than control group with p. value 0.000*

Table 3 Serum IL-21 level in different groups of psoriatic patients

Serum IL-21 (pg/Ml)	**Sum of Squares**	**df**	**Mean Square**	**F**	**P. value**
Between Groups	336.000	2	168	**4.639**	**0.003***
Within Groups	1340.000	37	36.216		
Total	1676	39			

From the analysis of variance (ANOVA), there was a significant relation between means of serum level of IL-21 in different groups with P.value =0.003*.

Table 4 Correlation between serum level of IL-21and PASI score of psoriatic patients

	IL-21(pg/ml)	
	r.	**P. value**
PASI	0.68	**0.000***

There was a significant positive correlation between serum level of IL-21 and PASI score in psoriatic patients with P.value 0.000*

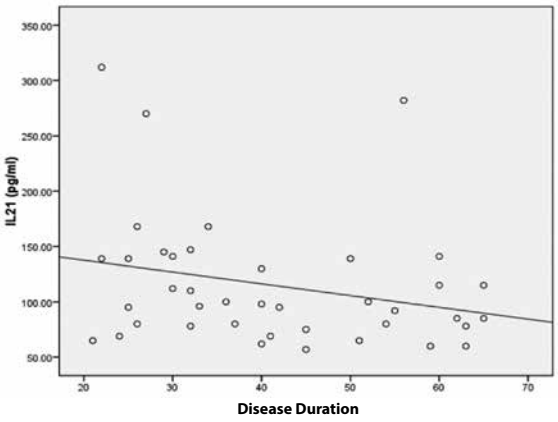

Fig. 1 Non-significant correlation between serum level of IL-21 and duration of disease (months) in psoriatic patients.

DISCUSSION

In order to achieve the aim of the study, the study included 40 patients with psoriasis were either newly diagnosed or stopped systemic treatment for four weeks prior to blood sample collection, had no other autoimmune or systemic disease and 25 healthy volunteers as controls.

The results of our study revealed that psoriatic patients had a statistically significant higher serum level of IL-21 than controls. Our finding is consistant with similar studies carried out by Nakajima et al,[11] and He et al,[12] as both studies reported higher levels of serum IL-21 in psoriatic patients than in normal controls.

Caruso et al,[9] reported that the levels of IL-21 were significantly elevated in all samples taken

from lesional psoriatic skin compared to samples taken from non lesional skin of the same individuals and from normal control individuals and its high-expression may be related to the pathogenesis of psoriasis.

In addition Monteleone et al,[8] reported that excessive IL-21 can lead to inflammation in many organs and the mode of epidermal hyperplasia and inflammatory infiltration induced by IL-21 in mice is similar to the pathological features found in plaque psoriasis. Hence, the elevation of IL-21 levels is an important component of complicated immune disorders as in psoriasis and is closely related with the occurrence and development of the disease.

In the current study a significant positive correlation was detected between serum level of IL-21 and the severity of psoriasis according to PASI score. This result suggested that serum IL-21 was a good marker of the clinical severity of psoriasis. This result was agreement with that of He et al,[12] and de Oliveira et a*l*,[13] they reported that serum IL-21 levels were positively correlated with PASI scores in the patients with psoriasis.

On the contrary, Nakajima et al,[11] reported that serum levels of IL-21 were not positively correlated with PASI scores. The reason for this discrepancy is due to difference in number of patients (40 in our study versus 30) also differences in ages, types, stages and medical history of the patients.

The nature of the stimulus driving IL-21 production in psoriasis is that IL-21 expression is genetically regulated, given that a region of chromosome 4q27 harboring the IL-21 gene is associated with psoriasis, and single nucleotide polymorphisms in this locus are associated with higher IL-21 levels in other immune-mediated disorders.[14]

Another possibility is that naive T cells recruited from the blood are induced *in situ* to make IL-21 in response to factors that preferentially drive Th1 or Th17 cell pathways, consistent with the demonstration that some of the IL-21 producing T cells infiltrating psoriatic plaques co express interferon (IFN) γ or IL-17, the signature cytokines of Th1 and Th17 cell responses respectively.[14]

Moreover, blockage of IL-21 with a human antibody reduces the epidermal thickness and the expression of inflammatory Th1 and Th17 genes in a clinically relevant human psoriasis xenograft mouse model. In this model, abundant proliferating keratinocytes are seen in mice treated with control but not anti-IL-21 antibody. These results collectively indicate a key role of IL-21 in promoting epidermal hyperplasia and inflammatory infiltration process, this finding may become the way for the use of anti IL-21as antipsoriatic agent.[15]

CONCLUSION

Serum level of IL-21 was increased in psoriatic patients in comparison to normal controls. IL-21 was positively correlated with severity of the disease evaluated by PASI score. IL-21 may play a major role in the pathogenesis and development of psoriasis and could be used as a marker for disease severity.

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