ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
April 2018; 17(2):179-187.

Evaluating Serum Levels of IL-33, IL-36, IL-37 and Gene Expression of IL-37 in Patients with Psoriasis Vulgaris

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Received: 25 April 2017; Received in revised form: 2 August 2017; Accepted: 10 August 2017

ABSTRACT

Serum levels of interleukin (IL)-33, IL-36 and IL-37 have been reported to be up-regulated in various T helper (Th)1/Th17 mediated autoimmune/inflammatory diseases. Although IL-33 and IL-36 expression are increased in skin lesions of patients with psoriasis, their serum levels in such patients have not yet been adequately studied. We aimed to evaluate serum level of IL-33, IL-36 and IL-37 cytokines and IL-37 gene expression in patients with autoimmune/inflammatory disease of psoriasis and to explore their correlation with disease severity. Such evaluation further clarifies disease pathogenesis and may be utilized in clinical practice.

47 patients with psoriasis vulgaris and 47 healthy individuals were included. Serum IL-33, IL-36 and IL-37 levels were measured by Elisa and gene expression of IL-37 measured by real time PCR in all participants. The disease activity was assessed by the psoriasis area and severity index (PASI). Linear Correlation between interleukin measures and PASI score was calculated. Also sensitivity and specificity of such measurements were determined.

Serum IL-36 and 37 levels in patients with psoriasis vulgaris were significantly higher than those in healthy controls and positively correlated with disease activity (PASI score). Serum IL-33 levels in patients were equal to those in healthy controls but positively correlated with disease activity. Serum IL-36 levels were significantly higher than serum IL-33 levels. Gene expression of IL-37 levels in patients were higher than healthy controls but was not correlated with disease activity.

Serum IL-36 and IL-37 levels are generally increased in psoriasis vulgaris and correlated with disease severity. Therefore, serum IL-36 and IL-37 levels may be markers of treatment and diagnosis of psoriasis.

Keywords: IL-33; IL-36; IL-37; Psoriasis, Psoriasis area and severity index (PASI) score

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Published by Tehran University of Medical Sciences (http://ijaai.tums.ac.ir)

INTRODUCTION

Psoriasis is a chronic, proliferative, congenital and inflammatory skin disease characterized by raised, red scaly plaques.[1] The disease prevalence is about 2-3% of the world-wide population[2] associated with several co-morbidities such as cardiovascular complications.[3] Although psoriasis develops by chronic interactions between hyperproliferative keratinocytes and infiltrating activated immune cells,[4] its definite pathogenesis remains not clear. However, evidences have indicated that some kinds of imbalances between pro- and anti- inflammatory cytokines play important roles.[5] For example, one study has revealed the association of psoriasis with different cytokines of tumour necrosis factor (TNF), IL-22 and IL-17.[6]

IL-33 is known as an inflammatory member of IL-1[7] which is released from cells undergoing necrosis[8] and binds to cells containing its receptor, ST2 receptor, such as mast cells, eosinophils and Th2 cells.[9] Binding to Th2 cells, IL-33 plays an essential role in Th2-driven diseases like atopic dermatitis, asthma and allergy.[9] This activity of IL-33 could be generated by production of IgE from B cells and IL-4, IL-5, and IL-13 cytokines fromTh2 cells in which IL-33 triggers the induction of GATA3 and signal transducer and activator of transcription 5 (STAT5).[10]

It has been shown that IL-33 is increased in skin lesions of psoriatic patients[11] and also in serum of some inflammatory/autoimmune diseases such as rheumatoid arthritis,[12] and inflammatory bowel disease (IBD)[13] correlated with severity of them.[13,14]

IL-36 is the other member of IL-1 family that is produced by skin keratinocytes, bronchial epithelium, monocyte and lymphocytes;[15] and it mainly acts on T-cells and dendritic cells.[16] Conducting their inflammatory roles, all 3 forms of IL-36, named IL-36-α, IL-36-в and IL-36-ϒ, are agonistically able to activate the MAPK and JNK through IL-36R[17] which targets the promotor of IL-8 and leads to secretion of IL-6.[18] Elevation of IL-36 has been shown in psoriatic skin lesions.[6,19] An association of IL-36 has been found with one form of psoriasis, generalized pustular psoriasis, which is more severe than psoriasis vulgaris.[20,21]

IL-37, an anti-inflammatory member of IL-1 family,[22] is produced by peripheral blood mononuclear cells (PBMCs) and dendritic cells (DCs) under induction of several toll-like receptor (TLR) agonists and pro-inflammatory cytokines such as IL-1β, interferon (IFN)-γ, and TNF-α.[23] IL-37 may play an important inhibitory role in the development of inflammatory diseases. The serum levels of IL-37 in plasma of rheumatoid arthritis patients were significantly higher than healthy controls.[24] Psoriatic lesions express higher IL-37 than skin of healthy individuals.[25] In addition, serum IL-37 levels and the expression of IL-37 mRNA in PBMCs are much higher in patients with ankylosing spondylitis,[26] Graves' disease[5] and systemic lupus erythematosus[27,28] compared to those in healthy controls.

Stimulation/inhibition of the innate immune system respond could be one of the main therapeutic strategies in the treatment of psoriasis in close future. From one point, since there are limited studies on serum level of IL-33, 36 and no studies on IL-37 in patients with psoriasis and on the other hand, the pathogenesis of psoriasis is ambiguous, we aimed to evaluate serum level of IL-33, IL-36 and IL-37 and gene expression of IL-37 in such patients. If the changes of such cytokines be significant in psoriasis, our study may confirm their effect on the severity of psoriasis. In addition, a pharmacological block or stimulation of them may be effective in treatment of the disease.

MATERIALS AND METHODS

Patients

This case-control study was performed on 47 psoriasis patients in remission phase. All patients were randomly selected from the dermatology clinic of Kashan's Shahid Beheshti hospital. Exclusion criteria were smoking, using corticosteroid drugs and having other chronic inflammatory or autoimmune diseases. In addition, 47 healthy volunteers without a family history of psoriasis and other autoimmune as well as inflammatory diseases were enrolled as control group. The study protocol was conformed to the ethical guidelines of the 1975 Helsinki Declaration (N. 94018, 94023). Written informed consent obtained from all participants.

Disease Severity Measurement

The disease activity of psoriasis was evaluated by the psoriasis area and severity index (PASI).It is divided to mild, moderate and severe categories based on the scores taken by the patient according to the surface area involvement of 4 body regions including

head, trunk, lower and upper limbs and their histo-clinical profiles of desquamation, infiltration and erythema.[29]

Sampling and Experiments

Serum samples were collected from peripheral veins. Serum levels of IL-33, IL-36, and IL-37 were measured using available enzyme-linked immunosorbent assay (ELISA) kit (My Biosource, USA) according to the manufacturer's directions. Fresh peripheral blood mononuclear cells (PBMCs) were separated from 2 mL of anticoagulated blood by Ficoll-Hypaque (Lymphodex, Inno-Train, Germany) density gradient centrifugation. Gene expression assay was conducted by real-time PCR. Total RNA was extracted from PBMC using High Pure RNA Isolation Kit, Cat No: 11828665001, Roche Applied Science, cDNA synthesized from the extracted RNA using Transcriptor First Strand cDNA Synthesis Kit, Cat No: 04897030001, Roche Applied Science. The amount of IL-37 gene expression was measured through Taqman primer probe Comparative ΔCT method using ABI 7300 Real-Time PCR system as previously described.[30]β-actin housekeeping gene was used as endogenous control.

Statistical Analysis

The serum levels of IL-33, IL-36, and IL-37 and gene expression of IL-37 were analysed by independent t and chi-square tests. Correlations between variables were calculated by Pearson's correlation coefficient. Simultaneous effects of various factors on such cytokines were analysed by multiple linear regressions with backward method. $p<0.2$ was considered as exclusion criterion from the model. Adjusted R Squared was determined as a criterion of goodness-of-fit the model. Using ROC and Area under Curve (AUC), we tried to determine the specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) of those inflammatory markers in the diagnosis of psoriasis. Data were expressed as mean ± standard deviation (SD) and analysed by SPSS16software (SPSS Inc, SPSS Inc., Chicago, USA). $p<0.05$ was considered statistically significant.

RESULTS

Basic and clinical characteristics of psoriasis patients and healthy group are presented in Table 1. The serum levels of IL-36(50.52±31.06 versus34.12±20.35, *p* value=0.007), IL-37(49.35±19.96 versus41.06±15.12, *p* value=0.027) and gene expression of IL-37(9.33±2.31 versus7.41±1.94, *p* value<0.001) in patients were significantly higher than those in controls.

Table 1. Basic and clinical characteristic of psoriatic patients and healthy subjects being evaluated in terms of IL-33, IL-36, IL-37 serum levels and gene Expression of IL-37

		Psoriasis patients	Health subjects	*p* value
Number of subjects		47	47	-
Sex (Male/female)		15.32	18.29	0.517
Age (years)(Mean±SD)		33.83±11.93	30.17±4.82	0.09
Family history	Positive	14(29.8)		
	Negative	33(70.2)		
Disease duration (years)		13.64±9.1		
Number of patients with different PASI Score (%)	Mild (0-10)	38(80.9 %)	-	
	Moderate(11-19)	4(8.5%)		
	Severe(>19)	5(10.6%)		
BMI		25.88±3/79	25.2±3.64	0.1
IL-33 serum level (pg/mL)		19.21±9.43	19.30±6.58	0.954
IL-36 serum level (pg/mL)		50.52±31.06	34.12±20.35	0.007
IL-37 serum level (pg/mL)		49.35±19.96	41.06±15.12	0.027
IL-37 gene expression (pg/mL)		9.33±2.31	7.41±1.94	<0.001

PASI: Psoriasis area and severity index, BMI: Body mass index

Association of Serum Levels of IL-33, IL-36, and IL-37 and Gene Expression of IL-37 with Basic and Clinical Characteristics of Psoriatic Patients

The psoriasis patients were divided into different groups according to PASI score, sex, family history, disease duration and age (Tables 2, 3). There was a significant association between IL-33 and IL-36 serum levels with disease severity (p<0.001) (Table 2). Also, the serum levels of IL-37 were significantly higher in patients based on disease severity (p=0.008). There was no significant difference between gene expressions of IL-37 according to PASI score in patients' group (p=0.667) (Table 3).

Correlation of Serum levels of IL-33, IL-36 and IL-37 and Gene Expression of IL-37 with Different Parameters in Psoriatic Patients

Correlation between the serum levels of IL-33, IL-36, and IL-37 and gene expression of IL-37 with PASI, body mass index (BMI), age and disease duration in psoriatic patients showed a meaningful correlation between IL-33, IL-36 and IL-37 serum levels with PASI score. The most powerful relation was evaluated in the case of IL-36 serum level with PASI score (Table 4).

Table 2. Values of IL-33 and IL-36 serum levels according to different varieties in psoriatic patients

variables	status	IL-33 (pg/mL)	*p* value	IL-36 (pg/mL)	*p* value
Age	<20	19.39±1.77	0.813	29.20±22.06	0.002
	20-39	18.96±9.13		53.03±31.77	
	>39	19.63±11.15		50.10±31.22	
Disease duration (years)	0-10	18.29±8.64	0.438	43.26±23.00	0.272
	11-19	18.78±8.36		61.10±39.45	
	>19	22.58±13.49		49.32±29.28	
Sex	Male	19.48 ± 8.04	0.920	50.54 ± 31.37	0.047
	Female	19.30 ± 8.15		38.75 ± 24.30	
Family history	No	19.09±8.45	0.700	54.07±32.61	0.315
	Yes	20.27±11.82		44.04±26.44	
PASI Score (%)	Mild (0-9.9)	16.03±7.13	<0.001	40.40±22.11	<0.001
	Moderate (10-19.9)	31.83±7.69		72.83±11.46	
	Severe(>20)	32.60±4.63		107.53±29.13	

PASI: Psoriasis area and severity index,

Table 3. Values of IL-37 serum level and its gene expression according to different variables in psoriatic patients

variables		IL-37 serum levels (pg/mL)	*p* value	IL-37 gene expression (pg/mL)	*p* value
Age	<20	51.80±17.55	0.217	10.00±2.00	0.242
	20-39	47.67±20.14		9.46±2.40	
	>39	52.00±20.99		8.93±2.28	
Disease duration (years)	0-10	45.30±17.66	0.159	9.32±2.23	0.958
	11-19	48.95±18.95		9.06±2.26	
	>19	61.31±25.32		9.88±2.80	
Sex	Male	44.92 ± 17.29	0.923	8.62 ± 2.28	0.488
	Female	45.30 ± 18.37		8.27 ± 2.33	
Family history	No	48.31±18.27	0.586	9.03±2.06	0.156
	Yes	51.80±23.41		10.07±2.67	
PASI Score (%)	Mild (0-9.9)	45.04±16.94	0.008	9.24±2.17	0.667
	Moderate (10-19.9)	67.54±24.95		9.00±2.83	
	Severe(>20)	66.74±23.53		10.20±3.27	

PASI: Psoriasis area and severity index,

Linear multiple regression analysis showed that the factors of BMI, serum levels of IL-33 and IL-36 have a positive effect on PASI score. Such model showed a mainly high goodness-of-fit (Adjusted R^2=0.64) (Data not shown).Modelling the effects of serum levels of IL-33, IL-36 and IL-37 on psoriasis severity, we also found a high goodness-of-fit (Adjusted R^2=0.623) (Data not shown). Furthermore, we indicated that the combination of serum levels of IL-36 and IL-37 show a proper criterion in the evaluation of psoriasis severity (Adjusted R^2=0.608) (Table 5).

Cut-off Points and Predictive Values

Using ROC curve and AUC, we tried to determine the sensitivity and specificity of IL-33, IL-36 and IL-37 serum levels and IL-37 gene expression as diagnostic markers of psoriasis (Figures 1 and 2, Table 6). The most specificity was found in the cut-off point of IL-36=25.4, and the most sensitivity was found in the cut-off point of IL-37 gene expression= 7.5.

Table 4. Correlation between the serum levels of IL-33, IL-36, and IL-37 and gene expression of IL-37 with each other and different characteristics of the psoriatic patients and interleukins

	IL-33 (*p* value)	IL-36 (*p* value)	IL-37 (*p* value)	IL-37 gene expression (*p* value)
PASI	0.605 (<0.001)	0.763 (<0.001)	0.482 (0.001)	0.071 (0.633)
BMI	0.010 (0.924)	0.220 (0.033)	0.145 (0.163)	0.152 (0.144)
Disease duration	0.231 (0.118)	0.179 (0.229)	0.342 (0.019)	0.035 (0.814)
Age	0.060 (0.563)	0.268 (0.009)	0.137 (0.187)	0.201 (0.052)
IL-33 serum level	1	0.34 (0.001)	0.30 (0.003)	-0.15 (0.14)
IL-36 serum level	0.34 (0.001)	1	0.25 (0.015)	0.03 (0.74)
IL-37 serum level	0.30 (0.003)	0.25 (0.01)	1	0.16 (0.12)
IL-37 gene expression	-0.15 (0.14)	0.03 (0.74)	0.16 (0.12)	1

PASI: Psoriasis area and severity index,

BMI:Body mass index

Table 5. Coefficients multiple linear regression model for evaluation of psoriasis severity by PASI score

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	Adjusted R square
		B	Std. Error	Beta			
2	(Constant)	-8.626	2.507	----	-3.441	.001	0.608
	IL_36	.213	0.031	0.678	6.787	.000	
	IL_37	0.109	0.049	0.222	2.223	.031	

a. Dependent Variable: PASI score

Table 6. Sensitivity, specificity and predicting values of IL-33, IL-36 and 37 serum levels and IL-37 gene expression in psoriasis diagnosis

Variable	Cut point	Sensitivity (%)	Specificity (%)	Positive predicting value (%)	Negative predicting value (%)	Area under curve
IL-33 serum level	30.27	19.1	93.6	75	53.7	0.471
IL-36 serum level	25.40	83	42.6	59.1	71.4	0.665
IL-37 serum level	53.5	42.6	85.1	74.1	59.7	0.609
IL-37 Gene expression	7.5	85.1	55.3	65.6	78.8	0.736

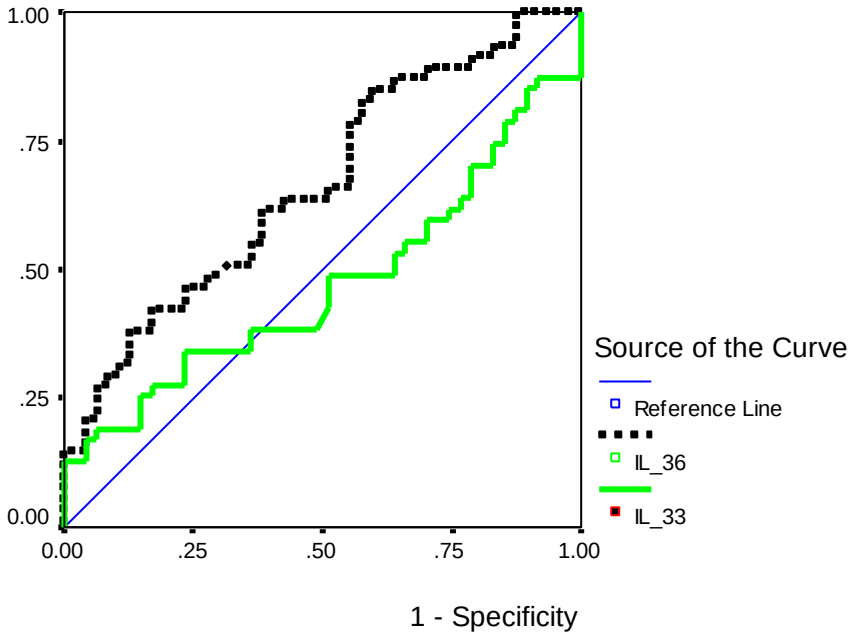

Figure 1. Sensitivity and specificity of IL-33 and IL-36 in psoriasis diagnosis

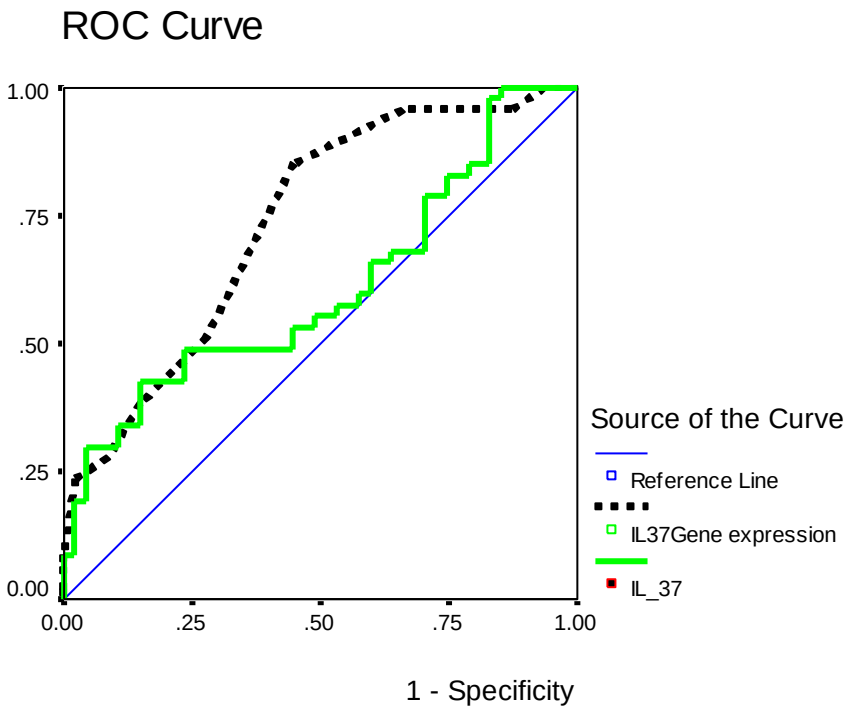

Figure 2. Sensitivity and specificity of IL-37 and gene expression of IL-37 in psoriasis diagnosis

DISCUSSION

IL-36 and IL-37 serum levels and IL-37 gene expression of PBMCs were significantly higher in our psoriatic patients than those in healthy controls. More importantly, our results showed a positive correlation between the serum levels of IL-33, 36 and 37 with disease severity. Previous studies have reported increased IL-33 levels in psoriatic lesion[11,31,32] as well as serum of psoriatic patients.[33] IL-33 is a known inducer of inflammatory cytokine of IL-6 in mast cells, and the number of IL-33$^+$ cells is increased significantly in Köbner positive dermal skin.[34] Such lesional elevation has been also showed in the case of IL-36.[6,35]

Considering inflammatory/anti-inflammatory effects of IL-36/IL-37, we may conclude involvement of such cytokines in the modification of inflammation in psoriasis. A growing number of studies have indicated that IL-37 inhibits inflammatory reactions in autoimmune diseases in which it is commonly associated with disease severity.[36,37] IL-37 can reduce the symptoms of colitis[25] and psoriasis[34] by inhibiting the expression of inflammatory cytokines such as IL-33. Increased serum level of IL-37 in our psoriatic patients and also increased its gene expression in systemic lupus erythematosus patients[28] correlated to disease severity[27] should be considered as a compensatory response not yet enough to alleviate the inflammatory state of the disease. Such correlation may confirm that such compensation starts at intracellular level and non-interferingly continues at serum level. Actually, since serum levels of anti-inflammatory marker of IL-37 in our study showed positive correlations with psoriasis severity, it seems that such marker may counterpart inflammatory effects of IL-33 as well as IL-36, and in this way it could improve the skin function of the patients. Yanmei et al demonstrated significantly lower IL-37 serum levels in IBD patients than those in healthy controls. However, IL-37 gene expression was higher in those patients and its serum levels were inversely correlated with disease severity.[38]

Since there are some challenges accompanying current assessment tools of psoriasis diagnosis, we designed different models containing different combinations of the mentioned inflammatory markers in the diagnosis of psoriasis. Having compared different models, we found that each lonely marker of IL-33, IL-36, IL-37 serum level as well as IL-37 gene expression shows a low strength in the diagnosis of psoriasis. It means that we need to apply statistical methods such as discriminant analysis,generalized linear model or latent profile analysis to evaluate the combinatory effects of such measurements in the diagnosis of psoriasis. Moreover, assessing the effect of any variable on severity of psoriasis, we should use multivariate ordinal logistic. Such analyses will be explained in our next article.

However, we indicated that the combination of serum levels of IL-36 and IL-37 shows a proper criterion in the evaluation of psoriasis severity by PASI score, especially considering that such combination lacks evaluating the IL-33 serum level and IL-37 gene expression whose measurements are more expensive and are not done routinely in most laboratories.

The limitation of our study was that firstly, we did not monitor the changes of selected cytokines longitudinally. This limitation allowed just a cross-sectional analysis of cytokine profiles of only limited robustness. Secondly, functional assays, which provide further information on molecular mechanisms of such inflammatory and anti-inflammatory cytokines, were not performed. However, our study may provide deeper insights into the functional role of IL-1 family in the control of psoriasis.

Our finding shows that serum level of IL-36 and IL-37 and gene expression of IL-37 elevate in psoriatic patients. Such measurement may be a tool to assess the disease severity and also it may be a reflection of disease diagnosis.

ACKNOWLEDGEMENTS

This work was supported by Deputy of Research, Kashan University of Medical Sciences, Kashan, Iran (grants No.94018 and 94023).

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