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The Comparison of Interleukin-17 and Interleukin-10 with Systemic Lupus Erythematosus Disease Activity

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Abstract

AIM: This study was conducted to compare means of interleukin-17 (IL-17) (Th17 cytokines) and interleukin-10 (IL-10) (T-regulatory cytokines) as pro-inflammatory and anti-inflammatory cytokine with disease activity of systemic lupus erythematosus (SLE) and to investigate correlation between IL-17 cytokine serums with IL-10 in SLE patients.

METHODS: This study recruited total of 68 SLE patients which included 34 active and 34 inactive patients based on MEX-SLEDAI as disease activity tool measurement and subjects were selected using consecutive sampling method. Blood samples were taken from subjects and IL-17 and IL-10 were measured using ELISA method. Data were analyzed with SPSS 26 software.

RESULTS: Mean IL-17 was 19.67 ± 1.299 pg/ml in active SLE group and 19.78 ± 1.187 pg/ml in inactive group. Median of IL-10 in active group was 3.63 pg/ml and in inactive group was 2.52 pg/ml, respectively. No significant mean differences were found of IL-17 and IL-10 between active and inactive SLE patients ($p > 0.005$). We found significant positive correlation between IL-17 and IL-10 ($p < 0.005$; $r = 0.529$).

CONCLUSION: There were no significant mean differences of IL-17 and IL-10 between active and inactive SLE patients. However, we found elevated result of IL-10 in active SLE than inactive. There was positive correlation between IL-17 and IL-10.

Introduction

The occurrence of this disease is a result of interactions between genetic, environmental, and hormonal, causing immunological disorders. T lymphocyte cells (CD4+) play an important role in the occurrence of autoimmune diseases. During T cell receptor activation, naive CD4 cells can differentiate into T-helper (Th)1, Th2, Th17, and T-regulator (T-reg) cells based on the production patterns and cytokine function of each T-helper cell. In SLE, this imbalance of T-helper cell cytokines is also thought to contribute to the pathogenesis of SLE [3], [4], [5].

Th17 cells produce cytokines interleukin-17 (IL-17) which acts as protection in host cells, but excessive activity can lead to autoimmune and inflammatory conditions. Recent studies also showed that homeostatic disorders that occur in autoimmune are also caused by disruption of the regulator's function, which are T-reg cells that produce cytokines interleukin-10 (IL-10). The Th17/T-reg subset is slowly replacing the old paradigm of the relationship between B cells and the Th1/Th2 subset in autoimmunity. The balance between the activity of immune regulation and inflammation of the Th17/T-reg cell subset is absolutely necessary in maintaining optimal immunity so that interference with this subset will lead to autoimmune diseases, especially SLE [6], [7], [8].

Role of the Th17 and T-regulator axis of SLE disease activity still shows controversial results. Research on IL-17 as a cytokine produced by a subset of Th17 and IL-10 as a T-reg cytokine in SLE disease activity still shows different results [9], [10].

This study was conducted to compare means of IL-17 (Th17 cytokines) and IL-10 (T-regulatory cytokines) as pro-inflammatory and anti-inflammatory cytokine with disease activity of SLE and to investigate correlation between IL-17 cytokine serums with IL-10 in SLE patients.

Methods

This study recruited total of 68 SLE patients which included 34 active and 34 inactive patients based on MEX-SLEDAI as disease activity tool measurement and subjects were selected using consecutive sampling method. Patients with infection, severe systemic events, and other autoimmune diseases are excluded from the study. Research sites are in outpatient Department of Allergy and Immunology – Internal Medicine in Cipto Mangunkusumo General Hospital in Jakarta. All patients have signed the informed consent. This research has received an ethical approval from the Ethics Committee of Medical Faculty of University of Indonesia.

Blood samples were taken from subjects and IL-17 and IL-10 were measured using ELISA method. All data are collected and tabulated then statistical analysis is computerized using the SPSS version 26. A value of $p < 0.05$ was considered as statistically significant.

Results

In this study, from 68 total samples, 100% female samples were obtained with a median age of 31 years with a minimum age of 18 years and a maximum age of 65 years. Age group 21–40 years is the most commonly found in this study, which is 81.8% and the least is the age group 20 years as much as 11.8%. Duration of SLE diagnosis in this study was obtained at most for >1 year by 82.4%. Disease activity based on the MEX SLEDAI score obtained a median of 1, with a minimum score of 0 with a maximum of 17. A total of 34 SLE patients (50%) were active LES and 50% patients were inactive LES. In this study, 85.3% of subjects did not use immunosuppressant, followed by 67.6% with single immunosuppressant, 50% combination of two immunosuppressant, and 2.9% combination of three immunosuppressant. The highest steroid dose equivalent to 4 mg/day was 54.4% and 10.3% were not on steroid therapy. The average IL17 level was 19.73 (1.24) pg/ml. The median IL-10 level is 2.96 pg/ml with a minimum level of 0 pg/ml and a maximum of 11 pg/ml. Table 1 shows the baseline characteristics of all samples.

Table 1: Baseline characteristics

Characteristics	n=68
Sex, n (%)	
Male	0 (0.0)
Female	68 (100.0)
Age (year old), median (min-max)	31 (18–65)
Age group, n (%)	
≤20 year old	8 (11.8)
21–40 year old	32 (81.8)
>40 year old	18 (26.5)
SLE duration, n (%)	
≤1 year	12 (17.6)
>1 year	56 (82.4)
Immunosuppressant, n (%)	
Without	29 (85.3)
Single drug	23 (67.6)
Two combinations	17 (50)
Three combinations	1 (2.9)
Steroid, n (%)	
Without	7 (10.3)
Dose ≤4 mg/hari	37 (54.4)
Dose >4 mg	24 (35.3)
MEX SLEDAI, median (min-max)	1 (0–17)
SLE	
Active	34 (50.0)
Inactive	34 (50.0)
IL-17 (pg/ml), Mean (SD)	19.73 (1.24)
IL-10 (pg/ml), median (min-max)	2.96 (0–11)

SLE: Systemic lupus erythematosus, IL: Interleukin, SD: Standard deviation.

From this study, a significant positive correlation was obtained between IL-17 and IL-10 levels in SLE patients with $p < 0.001$ and $r = 0.539$, as shown in Figure 1.

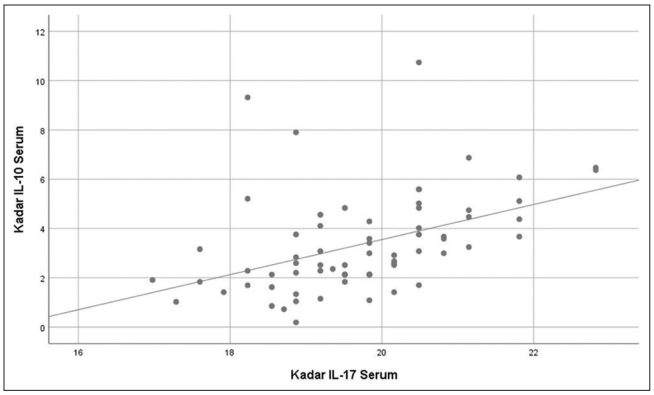

Figure 1: Correlation between interleukin-17 and interleukin-10 levels in systemic lupus erythematosus patients

This study shows that there is no significant mean difference between the IL-17 levels of the active and inactive SLE groups. IL-10 levels in active SLE were higher than inactive SLE but there were no significant differences between them (Table 2).

Table 2: Differences between IL-17 and IL-10 mean level with SLE disease activity

Variable	SLE		p
	Active	Inactive	
IL-17, mean (SD)	19.67 (1.299)	19.78 (1.187)	0.711
IL-10, median (min-max)	3.63 (1-11)	2.52 (0-6)	0.099*

SLE: Systemic lupus erythematosus, IL: Interleukin, SD: Standard deviation.

Discussion

In this study, there were 68 female subjects with SLE and no men with a median age of 31 years, and the most were between the ages of 21 and 40 years. Predomination of female sex is a characteristic of SLE disease as a systemic autoimmune disease, in which other studies showed the ratio of women/men is 9/1–10-15/1, which can reach its peak at productive age as shown in this study. The influence of hormonal, cytokine, and genetic imbalances is thought to play a role in the predominance of female sex in this SLE. High estrogen levels and low progesterone

in SLE affect the expression of toll-like receptor-17 mediated IFN-α and chemokine C-X-C ligand 10 in the peripheral so that it can cause disease progression and SLE disease activity through modulation of the IFN-α pathway [11], [12], [13].

The duration of SLE disease in this study obtained a median of 4.5 years with SLE disease >1 year more than <1 year (82.4% vs. 17.6%). This is consistent with research conducted by Kakati *et al*. which showed that SLE disease duration >1 year (71.7%) is more than <1 year (28.3%). The Almenara Lupus cohort study showed a longer average LES disease of 7.7 years. Disease activity in this study was calculated based on the MEX-SLEDAI score obtained a median of 1 with a minimum value of 0 and a maximum of 17. Based on the MEX-SLEDAI criteria, a score of <2 had mild activity, in this study categorized as an inactive SLE with a total of 34 subjects and scores >2 were categorized as active SLE with 34 subjects. In this study, the active SLE median obtained 8 with a minimum value of 2 and a maximum of 17. The use of MEX-SLEDAI used in this study to determine disease activity because based on research by Freire *et al*., MEX-SLEDAI has a higher validity than other measuring devices such as British Island Lupus Assessment Group and Systemic Lupus Activity Measurement and do not require a fee for their use [14], [15], [16].

The mean IL-17 level in this study was 19.73 (1.24) pg/ml. It was seen that IL-17 levels in SLE patients were higher than those of Talaat *et al*., Yao *et al*., and Tsanakti *et al*. with the mean IL-17 levels were 17.7 (2.3) pg/ml, 18.23 (8.22) pg/ml, and 9.08 (1.39) pg/ml, respectively. Research by Galil *et al*. showed almost the same results as this study, which is 19.47 (10.21) pg/ml and studies by Wong *et al*. and Vincent *et al*. showed a higher mean of IL-17, which are 76.5 (45.7) pg/ml and 140.6 pg/ml [17], [18], [19], [20], [21], [22].

This study also showed a correlation between IL-17 levels and IL-10 serum obtained a significant positive correlation with $p \leq 0.05$ and $r = 0.539$. It can be seen that the pro-inflammatory activity of IL-17 is significantly proportional to the secretion of IL-10 from T-reg cells in SLE patients. This is consistent with the hypothesis showing that IL-17 and IL-10 have a positive correlation in SLE. IL-10 as an anti-inflammatory cytokine has the characteristics of cytokines as cytokines T-regulator cells especially T regulator type 1 cells (Tr1) which under normal circumstances can inhibit the response of B cells which is an independent effect of IL-10. IL-10 itself is not only produced by T-reg cells but also produced by other T-helper cells that have regulatory functions, besides IL-10 is also a cytokine that plays a role in the maturation and differentiation factors of B cells, so as to increase survival, proliferation, isotype changes, and B cell differentiation to plasma cells [23], [24].

In SLE, IL-10 has a proven pathogenic role in this study correlating with IL-17 levels which activate the formation of autoantibodies (autoreactive B cells) which have an impact on increasing disease activity and severity of SLE. A study by Facciotti *et al*. showed that mice with SLE secreted IL-10 by T-regulator cells and follicular T-helper (Tfh) cell populations which showed that in addition to T-regulator cell activity, autoreactive B cells also express pathogenic cytokines IL-10 spontaneously which induces the formation of autoantibodies *in vitro*, as well as the production of autoantibodies in mice *in vivo*, which until now the pathophysiological mechanism is still being investigated further, especially the role of follicular T-helper cells in the balance of Th17/Treg cells and Th1/Th2 cells. Analysis of IL-10 secretion in other T cell subsets has also not been able to identify the unique cellular role of these cytokines. The paradoxical pathogenic activity of IL-10 in SLE is still interesting to study considering that the capacity of IL-10 has not yet been identified that independently stimulates the production of autoantibodies, so it is suspected that there is involvement of other T-set subset pathways that contribute to this stimulation. A study by Su *et al*. demonstrated the involvement of microRNA (miRNAs) in the stimulation of IL-10 in SLE. The dysregulation of miR-199-3p expression increases IL-10 production which targets Poly (ADP-ribose) polymerase-1 which is a serological marker found in SLE patients and is associated with inflammatory factors and cytokines, but the role of miRNA in the pathogenesis of SLE is still being evaluated, especially its impact on the clinical and activity of SLE disease [23], [24], [25], [26].

This study showed that there is no difference in the mean IL-17 serum levels of active and inactive SLE patients. This result is different from study conducted by Talaat *et al*. and Galil *et al*. which showed a significant mean difference between the IL-17 levels of active and inactive SLE patients, while the study of Zhao *et al*. which involved 41 active and 16 inactive SLE patients showed no significant mean difference between the two groups. The study conducted by Yao *et al*. showed that there was a mean difference between active and inactive SLE with $p = 0.041$ although it was not related to disease activity score (SLEDAI). Yao *et al*. also classifying between active SLE with neuropsychiatric lupus involvement (NPSLE) and without NPSLE found no significant difference (18.23 and 18.77 pg/ml). The comparison between IL-17 levels in active and inactive SLE patients still show different results in each study. Previous study has involved healthy controls as a comparison, in which it showed that active SLE patients secrete IL-17 influenced by the induction of adhesion molecules such as cell surface cadherin, integrin, selectins, ICAM-1, and VCAM, which when compared with controls healthy will show results of higher IL-17 levels, thus allowing the role of lymphocytes and antigen-presenting cells in the development of autoimmune responses, but studies in the inactive SLE group have not been conducted yet. In addition, defects in the development and activity of regulator T-CD4 cells both in terms of quantity and quality also affect the ability

of cells to suppress the proliferation and production of IL-17 proinflammatory cytokines in immune cell effector in SLE patients, so there is a possibility that IL-17 can contribute to the ability of T-regulator cell inhibition due to reciprocal control in the formation and supervision of Th17 cells and T-regulator cells [17], [18], [19], [27].

The results of this study also showed no mean difference between IL-10 active and inactive SLE patients, but a median serum IL-10 value was higher in the active group than inactive. In addition, IL-10 levels also showed higher results than inactive SLE. Serum IL-10 was also found to be higher in the study of Koenig *et al*. that conducted in the SLE group with active nephritis compared to inactive and control SLE, although the sample used was limited to 12 subjects. A study by Godsell *et al*. involving 129 active SLE patients who underwent IL-10 examination at the first visit and continued 2 years later showed that serum IL-10 could be a predictive factor for the possibility of relapse in SLE patients. In the study, it was mentioned that patients with the highest quartile at the time of initial diagnosis of SLE had a 3.6-fold potential to experience active SLE in subsequent controls, and this result also correlated with SLE inflammatory markers such as erythrocyte sedimentation rate, anti-dsDNA, levels C3 and C4, and significant correlations were also obtained at the next SLE patient visit, so from this study it was seen that serum IL-10 levels might be a marker of disease activity in SLE patients [28], [29], [30].

Conclusion

There were no significant mean differences of IL-17 and IL-10 between active and inactive SLE patients on this study. However, we found elevated result of IL-10 in active SLE than inactive which described the activity of anti-inflammatory cytokines produced by T-regulatory cells were higher in active SLE. There was positive correlation between IL-17 and IL-10.

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