IL-23IL-17 axis and disease activity in systemic lupus erythematosus patients

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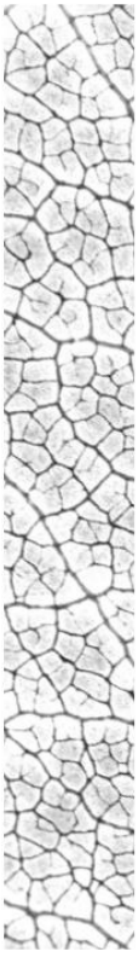

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IL-23/IL-17 axis and disease activity in systemic lupus erythematosus patients

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Abstract

Introduction: The latest paradigm proposes that imbalance of Treg and Th17 cells play a significant role in Systemic Lupus Erythematosus (SLE) pathogenesis. The influence of IL-23 and IL-17 on the pathogenesis of SLE remains controversial. This study aimed to observe the role of IL-23/IL17 axis in the pathogenesis of SLE as disease activity using Systemic Lupus Activity Measure (SLAM) index.
Methods: This cross-sectional study analyzed thirty blood serum specimens taken from female patients with SLE diagnosed by the 1997 ACR criteria. All samples were analyzed for IL-23 and IL-17 serum level using ELISA method. Pearson's/Spearman's correlation test and Path analysis were used for statistical analysis.
Results: Thirty female subjects aged 31.3±10.46 years all manifested with hematology abnormalities and arthritis posed as the most common clinical manifestation. Both IL-23 and IL-17 levels increased at 625.33 pg/mL and 34.53 pg/mL, respectively. Disease activity resulted in a high mean SLAM score of 29.3±3.9. No correlation was found between serum IL-23 and serum IL-17 (r=0.089; p>0.05). Furthermore, IL-17 and IL-23 did not significantly correlate to disease activity (r=0.026; p>0.05); (r=0.116; p>0.05).
Conclusion: There was no significant correlation between IL-23 and IL-17 with SLE disease activity.

Keywords: SLE, disease activity, IL-23, IL-17

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease with a series of complex clinical manifestations that vary from mild to life-threatening (Bertsias et al. 2017, Jakes et al. 2012, Maule 2011). The number of patients with SLE keeps growing (Yanih 2016). In the USA, lupus incidence is estimated at 51 per 100,000 population. Women are nine times more influenced than men (Wuryana et al. 2016). The primary causes of mortality of SLE patients are the major organ insufficiency arising from active disease (flare), cancer, and heart failure (Patrick et al. 2018). While the exact cause of SLE is unclear, some genetic predispositions and associations between genes and the environment have been identified. Genetic risk factors, environmental causes, associations with B-cell and T-cell, antigen/Ab-responses and mechanisms of immune clearance combine to generate and maintain autoimmunity in SLE (Sibarani et al. 2018). SLE can cause systemic inflammatory symptoms, leading to permanent organ damage (Marpaung et al. 2018).

Biomolecular studies on SLE are thriving, yet there is still none that can clearly explain the exact pathogenesis of SLE (Leng et al. 2010, McCarthy et al. 2014, Shankar et al. 2014). As a result, it is quite difficult to diagnose SLE, to determine its disease activities, and to perform an immediate and precised patient management, both high SLE morbidity and mortality (Chaichian et al. 2013). Many clinicians have been running erythrocyte sedimentation rate (ESR) and C-Reactive protein (CRP) level tests as markers for acute phase as well as serological tests, such as anti-dsDNA level, anti-C1q antibody level, and C3-C4 complement level. CRP is also an independent risk factor for heart disease (Samad et al. 2019). However, these tests have been showing limited sensitivities and specificities (Birmingham et al. 2010). CRP is a well-established systemic marker for inflammation (Adam et al. 2006).

A new paradigm on SLE has emerged in which the SLE pathogenesis involves the imbalance of Treg cell

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anti-inflammatory agent and Th17 as proinflammatory agent (Handono et al. 2013). Th17 is a T-cell subtype which is has an important role in the pathogenesis of many autoimmune diseases, including SLE. It mainly produces IL-17 cytokine. The production of IL-17 itself depends on the presence of other cytokines like IL-23 (Du et al. 2014, Zickert et al. 2015). IL-23 stimulates the differentiation and the expansion of Th17 and maintain Th17 stability in producing IL-17 in SLE. This mechanism is known as IL-23/IL-17 axis, and lately, there have been many studies on its role to various autoimmune diseases including SLE (Du et al. 2014, Puwipirom et al. 2010, Zickert et al. 2015).

Data from various studies on the correlation of IL-23/IL17 axis and SLE hitherto remain controversial. The previous study reported that elevation of IL-23 and IL-17 levels occurs on patients with active SLE (Puwipirom et al. 2010, Zhang et al. 2009, Zickert et al. 2015). On the other hand, other studies found that IL-23 level only elevated on lupus nephritis and was not altogether correlated to SLE as a whole (Du et al. 2014). Furthermore, another study showed that the decrease of IL-22 level correlated to disease activity of SLE and not to IL-23 and IL-17 levels (Cheng et al. 2009). These conflicting results are likely to come up considering the variety in study methods, subjects' sampling methods, and genetic backgrounds. This study aimed to observe the role of IL-23/IL17 axis in the pathogenesis of SLE as disease activity using SLAM index.

MATERIALS AND METHODS

Subjects

This cross-sectional study involved 30 patients with naïve SLE aged sixteen to sixty years old who were hospitalized in the Internal Medicine Ward of Dr. Soetomo General Hospital, Surabaya, from April to July 2018. These subjects were sampled by consecutive sampling method. SLE patients were diagnosed using the 1997 American College of Rheumatology criteria for SLE in which patients must meet 4 out 11 criteria for SLE diagnosis. Patients with history of immunosuppressive agents or steroids medication, acute or chronic infections, malignancies, asthma, acute coronary syndrome, HIV/AIDS, inflammatory bowel disease, spondilo-arthropathy, overlapping syndromes, and active smoking were all excluded from study. Every patient who was enrolled in this study has voluntarily signed a consent form stating their willingness without force nor coercion to participate as study subjects. All study subjects were aware that they were involved in this cross-sectional study and their rights and confidentiality as patients were preserved with utmost respect. This study was conducted strictly according to the 2016 ICH-GCP and the Declaration of Helsinski and has been approved by Ethics Committee of Dr. Soetomo General Hospital, Surabaya.

Basic Hematology Evaluation and SLAM Index

All patients had their disease activities and their blood samples evaluated before underwent immunosuppressive therapy. Bloodwork was performed to evaluate complete blood count, ANA profile, anti-dsDNA level, and IL-23 and IL-17 levels. Disease activity was evaluated by Systemic Lupus Activity Measure (SLAM) index. It is a measuring tool for assessing SLE disease activity by scoring each parameter between 0-3. The total score is the sum of all parameters which ranges between 0 and 86. Higher score indicates more active or severe illness.

IL-23 and IL-17 Analysis

Blood sample for interleukines evaluation was drawn from the patient in the morning and in under 30 minutes must be sent to laboratory for centrifuge. The serum was stored in -80°C until it was ready for analysis. If the examination was done in less than 24 hours, the serum was stored at 2-8°C. When all 30 serum samples were collected and ready, IL-23 and IL-17 analysis was performed using Elabscience^{R} Coated ELISA Kit E-EL-H0107 Human IL-23 and E-EL-H01015 Human IL-17. A hundred microliter (µL) of standard or sample was added to each well and incubated for 90 minutes at 37°C. After the liquid was discarded, each well was added 100 µL of Biotinlated Detection Ab, incubated for 1 hour at 37°C, and then aspirated and washed 3 times afterwards. Next, they were added 100 µL of HRP conjugate, incubated for 30 minutes at 37°C, and again aspirated and washed 5 times afterwards. Finally, 90 µL of reagent substrate was put in and the wells were incubated for 15 minutes at 37°C before the addition of stop solution 50 µL. All the solutions in the wells were run through the color intensity immediately at 450 nm wavelength. The results were stated in picogram per millimeter (pg/ml).

Statistical Analysis

Data collected from this study was managed and analyzed in SPSS 21.0 program (IBM Corp., Armonk, NY, USA). Subjects' demographics and charactertics were shown as descriptive data. The statistical analysis was performed using Pearson's correlation test or Spearman's correlation test, with significance level of 0.05. Path analysis was used for further analysis

RESULTS

Subjects' Characteristics

Patients were all females aged 31.3±10.46 years old. SLE activities were recorded higher than 20 points by SLAM index at 29.3±3.9, with the lowest score of 22 and the highest of 37.

The subjects showed deviations in hematological component results (**Table 1**). Anemia by all cause (97%) was the most frequent disorder, followed by lymphopenia (90%) with 47% of severe lymphopenia.

Table 1. Subjects' Characteristics and Laboratory Results

Characteristics	Results (n=30)		
	n (%)	Mean	SD
Age		31.3	10.46
16-20	4 (13)	-	-
20-30	12 (40)	-	-
30-40 year	8 (27)	-	-
>40 year	6 (20)	-	-
BMI (kg/m^2)		18.8	2.42
Underweight	14 (46.67)	-	-
Normal	16 (53.33)	-	-
Hemoglobin (g/dL)	-	7.13	2.32
WBC (cells/µL)	-	8,055.67	3.442.18
Lymphocyte (cells/µL)	-	967.87	427.78
Platelet (cells/µL)	-	212,766.67	206,889.06
ESR (mm/hour)	-	61.83	38.18
CRP (mg/L)	-	30.16	59.45
C3 (mg/dL)	-	28.88	12.98
C4 (mg/dL)	-	16.95	11.72

Table 2. Subjects' Clinical Manifestation based on the 1997 ACR Criteria for SLE

Diagnostic criteria	Frequency
Malar rash	4 (13.3%)
Discoid rash	8 (26.7%)
Photosensitivity	13 (43.3%)
Oral ulcer	10 (33.3%)
Arthritis	23 (76.7%)
Serositis	14 (46.7%)
Renal disorder	8 (26.7%)
Neurologic disorder	6 (20.0%)
Hematologic disorder	
Hemolytic anemia	4 (13.3%)
Leukopenia < 4000/mm^3	1 (3.3%)
Lymphopenia < 1500/mm^3	27 (90.0%)
Trombocytopenia < 100,000/mm^3	12 (40.0%)
Immunologic disorder	
Negative anti-dsDNA (≤ 92.6 unit/mL)	16 (53.3%)
Positive anti-dsDNA (> 92.6 unit/mL)	14 (46.7%)
ANA *test*	
Negative (< 20 unit)	7 (23.3%)
Positive (≥ 20 unit)	22 (73.3%)

Thrombocytopenia (platelet count lower than 100,000 IU/microL) occurred in 40% of the subjects.

As shown in **Table 2**, the most frequent clinical manifestation shown in SLE subjects was arthritis (76.7%). On the other hand, renal disorder was the least manifested disorder in SLE subjects (26.67%). Furthermore, there were four patients (13.3%) with hemolytic anemia.

IL-23 and IL-17 Levels

This study showed elevations of IL-23 and IL-17 levels taken from all serum of active SLE patients. Median level of IL-23 serum was 625.33 pg/mL (48.13 – 3546.3 pg/mL) and median level of IL-17 serum was 34.53 pg/mL (0 – 530.35 pg/mL).

Correlation of IL-23, IL-17, and Disease Activity in SLE

Fig. 1 of statistical analysis shows that there is no correlation between IL-23 and IL-17 levels in this study (r=0.089, p=0.639).

Fig. 2 shows IL-17 IL-23 (r=0.116, p=0.543) serum levels showing any significant correlation to disease activity in SLE.

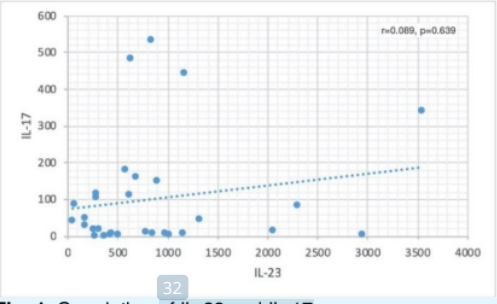

Fig. 1. Correlation of IL-23 and IL-17

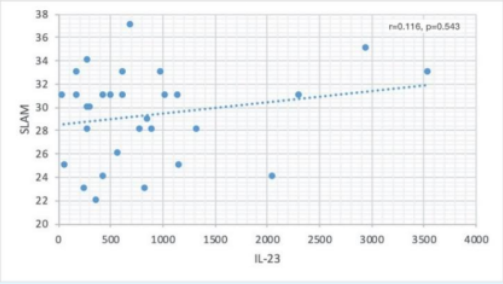

Fig. 2. Correlation of IL-23 and disease activity in SLE

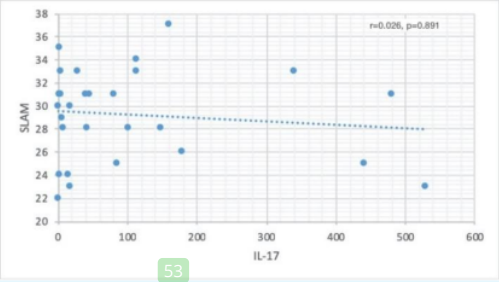

Fig. 3. Correlation of IL-17 and disease activity in SLE

Fig. 3 shows IL-17 (r=0.026, p=0.891) serum levels showing any significant correlation to disease activity in SLE.

Fig. 4 shows that path analysis is performed to analyze the dependencies among the three variables. The analysis resulted as non-significant. The effect of IL-23 on IL-17 was 0.18 (T-value=0.98<1.96), indicating that IL-23 level was not correlated to IL-17 level. Path analysis of both IL-23 and IL-17 effects on SLAM index score as disease activity also showed no dependency with 0.11 and -0.05 respectively (T-value=0.56 and -0.27). It meant that IL-23/IL-17 axis had no significant correlation to disease activity in SLE.

DISCUSSION

Recent studies have been showing the possibility of both IL-23 and IL-17 roles in the pathogenesis of SLE

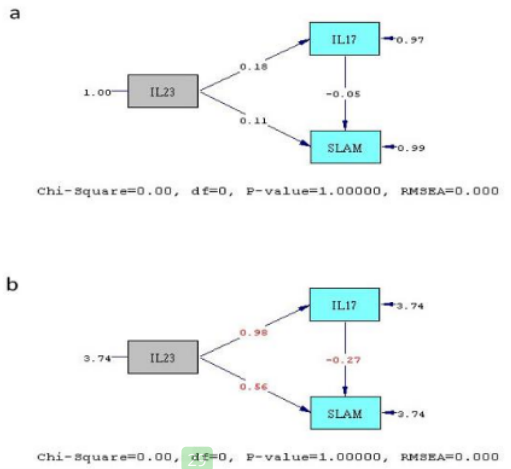

Fig. 4. Path analysis of IL-23/IL-17 axis on disease activity in SLE

due to the elevation of both interleukines found in active SLE patients. In this study, the median IL-23 level (625.33pg/mL) elevated compared to the normal median level of general Asian population (79.4 pg/mL) (Xia et al. 2015). This result is in accordance with previous studies conducted, in which the IL-23 level mostly elevated in patients with lupus nephritis with the median of 292.1 pg/mL and of 377 pg/mL, respectively (Wong et al. 2008, Xia et al. 2015). It indicates that IL-23 was involved in the SLE pathogenesis, especially in certain organ damages (Mok et al. 2010, Zickert et al. 2015). Based on normal IL-17 level in Asian population (4.5 pg/mL), the median of IL-17 level in this study (34.53 pg/mL) also elevated. This result is also supported by several past studies conducted in Swedish population, by another studies in Arabic population, and in Asian population showing various degree of elevation of IL-17 level from various samples (97.42 pg/mL, 18.55pg/mL, and 14.8 pg/mL, respectively) (Galil et al. 2015, Mok et al. 2010, Vincent et al. 2013, Zickert et al. 2015).

IL-23 is a pro-inflammatory interleukine enhancing Th17 proliferation and its mechanism in producing IL-17. The previous studies showed strong correlations between IL-23 and IL-17 levels in all SLE subjects, whilst a moderate correlation of IL-23 and IL-17 was reported by another studies (Oke et al. 2017). In contrast, this study was not able to prove any significant correlation between IL-23 and IL-17. There are many conditions that may cause this result. One of them is the influence or the interefence of other interleukines which on certain proportion might pose a synergic effect to the synthesis of IL-23 of IL-17. Besides, in addition to IL-23, IL-6 and IL-21 have ability to induce the production of IL-17 from Th17 cell (Crispín et al. 2010, Mak et al. 2014). Furthermore, another study reported a significant influence of IL-18 to the change of IL-23 and IL-17 levels (Wong et al. 2008). Along with IL-23, IL-18 can create a superimposedly elevate IL-17 level. There are other molecules too that might possibly alter the activation mechanism of Th17 and the production of IL-17 (Crispín et al. 2010, Wong et al. 2008). Moreover, disease progressivity among patients with active naïve SLE varies. Some may not have reached a condition in which IL-23 can optimally induce IL-17 production. In his animal trial, the previous study stated that IL-23 was suspected to have more role in maintaining IL-17 level constantly high in chronic SLE than inducing IL-17 production in active phase (Stritesky et al. 2008).

IL-17 is a potent pro-inflammatory cytokine that has been frequently studied for its significant correlations to disease activity of SLE (Ghanima et al. 2012, Moftah et al. 2016, Wong et al. 2008). The previous researcher attempted to correlate IL-17 level to specific organ damage in SLE, but meanwhile the patients showed high IL-17 level, the correlation between IL-17 and disease activity in SLE (using SLAM index) was not significant (Zickert et al. 2015). The other researcher also stated the non-correlation of IL-17 and disease activity using SLEDAI index and the negative correlation of IL-17 and IL-22, a fellow cytokine produced by Th17 (Cheng et al. 2009). A study reported that IL-17 was not correlated to disease activity evaluated by SLAM index but negatively correlated (-0.13) to SLEDAI-evaluated activity (Oke et al. 2017). Similarly, an Australia-based study showed with 39.9% subjects of Asian ethnicities, found no correlation of IL-17 and SLEDAI-evaluated disease activity in SLE (Vincent et al. 2013, Zhao et al. 2010).

Our previous study on Th-17/Treg ratio and its correlation to disease activity in SLE provided a supporting result to this study and Th17 appeared to have no significant correlation to SLAM-evaluated disease activity The fact that IL-17 is mostly produced by Th-17 gives a hint that there are possibly more dominant yet undetected, SLE-related, interleukins produced by other than Th-17. Some studies also showed insificant differences between IL-17 level in active and inactive SLE patients. It means that IL-17 presents in a steady level regardless of the SLE activity (Cheng et al. 2009, Martin et al. 2014, Tanasescu et al. 2010, Zhao et al. 2010). Furthermore, considering the role of IL-23 is more of maintaining the stability of IL-17 level rather than inducing IL-17 expansion, IL-23 could be having more important role in maintaining chronicity than causing lupus flares (Stritesky et al. 2008).

In this study, the strength of association between the three variables could not be determined due to correlation analysis did not come out as significant. There were many possible involved in molecular levels that could cause such result. IL-1β, IL-6, IL-8, IL-22 and TNF-α are among many other confounding factors in the pathogenesis of SLE (Cheng et al. 2009, Sabry et al.

2006, Wang et al. 2010, Yao et al. 2016). The fact that it was an in vivo non-experimental study, such factors are difficult to control. Genetic traits can also be one of the confounding factors, considering many past studies reporting the non-significant results involved more subjects from Asian ethnicities compared to non-Asians (Zhao et al. 2010). Furthermore, most of the studies evaluate disease activity in SLE using SLEDAI index, which may possibly cause distinct interpretation compared to SLAM index used in this study.

SLE is a heterogenous autoimmune disease whose clinical manifestations (especially involving major organs) vary in diverse populations. IL-23 and IL-17 levels do not always represent the systemic inflammation that occurs in SLE. However, they correlate better to certain major organ damage. Studies have shown that IL-17 is prominently accumulated in kidney or brain. The cross-sectional design for this study posed a limitation where the evaluation of all end-points (variables) was performed as a one-time only evaluation instead of a series of time-to-time observations. Besides, subjects were not categorized based on neither the progressivity of the disease (i.e. flare-up and chronic phase) nor certain major organ damage. Finally, neither IL-23 nor IL-17 serum level has a universal standard for their normal value as of yet.

CONCLUSION

Serum IL-23 and IL-17 levels elevated, but no correlation was found neither among both interleukines nor between their axis and disease activity in SLE patients. The roles of IL-23 and IL-17 in this group of SLE patients were imperceptible during active SLE but assumed to be dominant in its chronicity.

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Authors' Contributions

All of authors read and approved the final manuscript.

Ethics approval and consent to participate

Approved by the Ethics Review Committee (Approval number 0213/KEPK/IV/2018)

Consent for publication

Applicable

Availability of data and materials

Yes

Competing interests

The authors declare that they have no competing interests.

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