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 serum 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 cytokine serum with IL-10 in SLE patients (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 (Th1), 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 serum 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 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.

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.

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n/total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Female</td>
<td>68 (100.0)</td>
</tr>
<tr>
<td>Age (year old), median (min-max)</td>
<td>31 (18–65)</td>
</tr>
<tr>
<td>Age group, n (%)</td>
<td></td>
</tr>
<tr>
<td>≤20 year old</td>
<td>8 (11.8)</td>
</tr>
<tr>
<td>21–40 year old</td>
<td>32 (81.8)</td>
</tr>
<tr>
<td>&gt;40 year old</td>
<td>18 (26.5)</td>
</tr>
<tr>
<td>SLE duration, n (%)</td>
<td></td>
</tr>
<tr>
<td>≤1 year</td>
<td>12 (17.6)</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>56 (82.4)</td>
</tr>
<tr>
<td>Immunosuppressant, n (%)</td>
<td></td>
</tr>
<tr>
<td>Without</td>
<td>29 (85.3)</td>
</tr>
<tr>
<td>Single drug</td>
<td>23 (67.6)</td>
</tr>
<tr>
<td>Two combinations</td>
<td>17 (50)</td>
</tr>
<tr>
<td>Three combinations</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Steroid, n (%)</td>
<td></td>
</tr>
<tr>
<td>Without</td>
<td>7 (10.3)</td>
</tr>
<tr>
<td>Dose ≤4 mg/hari</td>
<td>37 (54.4)</td>
</tr>
<tr>
<td>Dose &gt;4 mg</td>
<td>24 (35.3)</td>
</tr>
<tr>
<td>MEX SLEDAI, median (min-max)</td>
<td>1 (0–17)</td>
</tr>
<tr>
<td>SLE</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>34 (50.0)</td>
</tr>
<tr>
<td>Inactive</td>
<td>34 (50.0)</td>
</tr>
<tr>
<td>IL-17 (pg/ml), Mean (SD)</td>
<td>19.73 (1.24)</td>
</tr>
<tr>
<td>IL-10 (pg/ml), median (min-max)</td>
<td>2.96 (0–11)</td>
</tr>
</tbody>
</table>

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 mean difference between the IL-17 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 between IL-17 levels in active and inactive SLE patients. 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].
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-regulator cells were higher in active SLE. There was positive correlation between IL-17 and IL-10.

References


17. Talaat RM, Mohamed SF, Bassyouni IH, Raouf AA. Th1/
PMID:25647269

PMID:26073684

PMID:27323066


PMID:23968496

22. Wong CK, Ho CY, Li EK, Lam CW. Elevation of proinflammatory cytokine (IL-18, IL-17, IL-12) and Th2 cytokine (IL-4) concentration in patients with systemic lupus erythematosus. Lupus. 2000;9(8):589-93. https://doi.org/10.1191/096120300678828703
PMID:11035433


PMID:31240224

PMID:31735515

PMID:30991045

PMID:19347604


PMID:22846145