ORIGINAL ARTICLE

Serum interleukin-18 levels in patients with systemic lupus erythematosus: Relation with disease activity and lupus nephritis

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Systemic lupus erythematosus; Interleukin-18; Lupus nephritis

Abstract  Aim of the work: To further investigate the possible role of IL-18 in the pathogenesis of systemic lupus erythematosus (SLE) and development of lupus nephritis (LN), and to explore its relationship with pathological classes of LN, degree of acute renal activity and chronic damage.

Patients and methods: Forty-one SLE patients with LN, thirty-one lupus non-nephritis patients and fifteen age and sex matched healthy controls were enrolled in this study. SLE patients were subjected to disease activity assessment by SLEDAI, renal disease activity assessment by the Systemic Lupus International Collaborating Clinics (SLICC) Renal Activity Score, laboratory investigations including measurement of serum interleukin-18 using Enzyme Linked Immunosorbent Assay. Renal biopsy was obtained from LN patients and pathological classification was made according to World Health Organization (WHO) criteria. Analysis of activity and chronicity indices was done on these biopsy specimens.

Results: Serum levels of IL-18 were significantly higher in patients with LN than lupus non-nephritis patients and healthy controls (p < 0.001). There were significant correlations between IL-18 and SLEDAI (p = 0.002), proteinuria (p = 0.027), renal activity score (p = 0.003) and activity index (p = 0.039) in patients with LN. There was no significant difference in the serum levels of IL-18 between WHO classes of LN.

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1. Introduction

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease with a complex pathogenesis involving multiple genetic and environmental factors. The disease is characterized by enhanced autoantibody production, abnormalities in function of immune-inflammatory system and inflammatory manifestations in several organs [1].

Lupus nephritis (LN) is a major complication of SLE that affects ~50% of patients. It is mediated by glomerular deposition of immune complexes that trigger a number of inflammatory events leading to tissue damage [2]. The presentation can range from asymptomatic urinary abnormalities to rapidly progressive renal failure leading to end-stage renal disease. Renal failure remains an independent risk factor for death in patients with LN [3].

Although the etiopathogenesis remains unclear, cytokine-mediated inflammation may occur in SLE [4]. A central pathological effect has been described for the inflammatory Th1 dependent cytokine IFN-γ. Production of IFN-γ is amplified by the cytokine IL-18, previously known as IFN-γ-inducing factor, in true synergy with other Th1-related cytokines, IL-2, IL-12, IL-15 and IL-23 [5]. IL-18 which belongs to the IL-1 cytokine family is predominantly produced by antigen presenting cells including macrophages and dendritic cells. It stimulates the production of inflammatory cytokines such as IFN-γ, TNF-α and IL-1β, upregulates chemokine production, enhances expression of adhesion and co-stimulatory molecules, enhances perforin- and FasL-mediated cytotoxicity by NK and T cells, and induces the release of matrix metalloproteinases, all activities that are central to the inflammatory reaction and subsequent tissue damage [6].

Accumulating evidence indicates that serum IL-18 levels are significantly elevated and correlated with disease activity in SLE [7]. Additionally, other studies have reported enhanced IL-18 renal expression in murine models of LN [8] and elevated levels of IL-18 transcripts in the biopsy specimens of kidneys from patients with LN [9]. In contrast, several studies have reached the opposite conclusions that the levels of serum IL-18 are irrelevant to disease activity and kidney involvement [10,11]. Thus, the functions of IL-18 in the pathogenesis of LN are still debated.

The aim of the present study was to further investigate the possible role of IL-18 in the pathogenesis of SLE and development of LN, and to explore its relationship with WHO pathological classes of LN, degree of acute renal activity and chronic damage.

2. Patients and methods

2.1. SLE patients and healthy controls

This study was conducted on 72 SLE patients recruited from the Department of Nephrology at the Mansoura Urology and Nephrology Center and Rheumatology and Rehabilitation Department, Mansoura University, Egypt. Diagnosis of SLE was established according to the American College of Rheumatology revised classification criteria for SLE [12]. SLE patients were divided into two groups according to the presence of renal involvement: 31 patients with no renal affection designated (lupus non-nephritis), and 41 patients with LN. Patients with LN were defined by persistent proteinuria > 0.5 g/24 h, or the presence of cellular casts, persistent hematuria or renal biopsy results consistent with LN [13]. Renal ultrasound was done for these patients at the start of the study to exclude other renal causes of kidney impairment. Patients with any of the following were excluded: diabetes mellitus, uncontrolled hypertension, overlap syndrome, malignancy, and chronic infections. Fifteen age and sex matched apparently healthy subjects served as control group.

An approval was obtained from the local ethics and scientific committees in addition to an informed consent from all participants in the study.

SLE patients were subjected to thorough history taking, general and local examination. Disease activity was assessed using the SLE Disease Activity Index (SLEDAI) [14]. Renal disease activity was measured by the Systemic Lupus International Collaborating Clinics (SLICC) Renal Activity Score. It was calculated as follows; proteinuria 0.5–1 g/day (3 points), proteinuria 1–3 g/day (5 points), proteinuria > 3 g/day (11 points), urine RBC’s > 5/hpf (3 points), and urine WBC’s > 5/hpf (1 point) [15].

Blood sample (5 ml) was extracted from each subject. Serum was isolated and stored frozen at ~80 °C for later ELISA experiment. Laboratory investigations included: full blood picture, ESR, CRP, serum creatinine, simple urine analysis & estimation of 24 h urinary protein, urine protein/creatinine ratio (P/C ratio), ALT, AST, C3, C4, ANA, and anti-dsDNA. Blood and urine samples were collected on the same day.

2.2. Measurement of serum IL-18

The RayBio® Human IL-18 ELISA kit (Cat#: ELH-IL18-001) was used for the measurement of serum IL-18 [16]. This assay employs an antibody (ab) specific for human IL-18 coated on a 96-well plate. 100 µl Standards and samples are pipetted into the wells and IL-18 present in a sample is bound to the wells by the immobilized ab. The wells are washed and 100 µl biotinylated anti-human IL-18 ab is added. After washing away unbound biotinylated ab, 100 µl horseradish peroxidase-conjugated streptavidin is pipetted into the wells. The wells are again washed, 100 µl tetra-methylbenzidine substrate solution is added to the wells and color develops in proportion to the amount of IL-18 bound. The Stop Solution (50 µl) changes the color from blue to yellow, and the intensity of the color is measured at 450 nm.

Conclusion: IL-18 appears to have a pathogenic role in the development of SLE and plays a crucial role in triggering inflammation in LN. Serum IL-18 levels could be a useful biomarker to assess the activity of renal disease in SLE.
2.3. Renal biopsy

It was obtained from all patients with LN at the start of the study for pathological classification of LN according to the criteria defined by the WHO [17]. The renal histopathological examination included light microscopic examination and immunofluorescence. The activity index (AI) and chronicity index (CI) of each biopsy specimen were also determined according to the previously accepted indices [18]. AI is the sum of semiquantitative manual scores (0–3 each) of the following parameters: endocapillary hypercellularity; leukocyte infiltration; subendothelial hyaline deposits; interstitial inflammation; fibrinoid necrosis and cellular crescents. Scores of the last two parameters are counted double, making a total CI of 0–24. CI is the sum of semiquantitative manual scores (0–3 each) of the following parameters making a total CI of 0–12: glomerular sclerosis; fibrous crescents; interstitial fibrosis and tubular atrophy. Evaluation of the biopsy specimens was performed by a single pathologist.

Statistics: Statistical analysis was performed using SPSS version 16.0 software. The description of the data was done in the form of mean ± standard deviation (SD) for quantitative data, and frequency & proportion for qualitative data. For quantitative data, “student’s r-test” was used to compare between two groups, and “one way ANOVA” to compare between more than two groups, followed by Bonferroni multiple comparisons. To test the association between variables, Pearson correlation co-efficiency test was used. P is significant if \(P \leq 0.05\) at confidence interval of 95%.

3. Results

Baseline characteristics of patients with LN and lupus non-nephritis patients are shown in Table 1. Fifteen healthy control subjects (12 females and 3 males, aged 35.92 ± 10.6 years) were recruited. All the three groups were age and sex matched.

3.1. Serum IL-18 levels in SLE patients

It was found that serum IL-18 levels were significantly higher in patients with LN and in lupus non-nephritis patients than in healthy controls (156.13 ± 57.96, 112.01 ± 48.23, 56.44 ± 23.59 pg/ml respectively, \(p < 0.001\)). Also, patients with LN had significantly higher levels of serum IL-18 than lupus non-nephritis patients (\(p < 0.001\)) (Fig. 1). In addition, no significant difference was found in the serum levels of IL-18 between male and female patients with SLE (160.00 ± 53.31, 132.56 ± 48.19 pg/ml respectively, \(p = 0.08\)). No significant correlation was also demonstrated between serum IL-18 levels and patient’s age, age at disease onset and disease duration (\(r = 0.04, 0.09, 0.10\) respectively, \(p > 0.05\)).

3.2. Association of serum IL-18 levels with disease manifestations

No significant difference was found in serum IL-18 levels between SLE patients with and without hematological involvement (161.20 ± 49.29, 143.72 ± 49.08 respectively, \(p = 0.137\)), with and without arthritis (127.55 ± 41.35, 139.71 ± 42.78 respectively, \(p = 0.245\)), or with and without pleuro-pulmonary involvement (137.72 ± 46.52, 134.41 ± 40.22 respectively, \(P = 0.760\)). However, SLE patients with central nervous system (CNS) manifestations (\(n = 39\) in the form of headache, psychosis and/or seizures had significantly higher serum IL-18 levels than patients without CNS manifestations (177.36 ± 67.08, 128.46 ± 55.28 pg/ml respectively, \(p = 0.01\)). It is worthy to note that 15 patients with CNS involvement had concomitant renal disease.

3.3. Correlation of serum IL-18 levels with SLEDAI, renal activity score, and laboratory findings

A significant correlation was found between serum IL-18 and the total SLEDAI score in all SLE patients (\(r = 0.346, p = 0.003\)) and in patients with LN (\(r = 0.461, p = 0.002\)), but not in lupus non-nephritis patients (\(r = 0.106, p = 0.572\)) (Fig. 2). Moreover, a significant correlation was found between serum IL-18 and anti-dsDNA abs titer in 72 SLE patients (\(r = 0.343, p = 0.003\)), and in patients with LN (\(r = 0.464, p = 0.002\)), while no significant correlation was demonstrated between them in lupus non-nephritis patients (\(r = 0.004, p = 0.981\)). In addition, a negative significant correlation was found between serum IL-18 and C3 (\(r = -0.5, p = 0.001\)) and C4 (\(r = -0.515, p = 0.001\)) only in patients with LN, while no significant correlation was found between serum IL-18 and ESR. Regarding laboratory findings assessing renal function, serum IL-18 of patients with LN showed a significant correlation with serum creatinine (\(r = 0.504, p = 0.001\)), 24 h urinary protein (\(r = 0.346, p = 0.027\)), and P/C ratio (\(r = 0.336, p = 0.032\)) (Table 2), and renal activity score (\(r = 0.46, p = 0.003\)).

3.4. Association of serum IL-18 levels with WHO classes of LN

By comparing the serum level of IL-18 in different classes of LN, it was found that the highest titers of serum IL-18 were detected in patients with class IV (167.01 ± 67.41 pg/ml) followed by class III (152.53 ± 46.01 pg/ml) then class II (121.90 ± 60.44 pg/ml) and the least titers were for class V (107.34 ± 60.66 pg/ml), but the difference was not statistically significant (\(p = 0.083\)) (Table 3). A positive significant correlation was demonstrated between serum IL-18 and AI of renal biopsy of patients with LN (\(r = 0.323, p = 0.039\)), while no significant correlation was found between serum IL-18 and CI (\(r = 0.25, p = 0.115\)).

3.5. Relation between serum IL-18 levels and medications

Patients with LN who received corticosteroids (CS) + cyclophosphamide (CYC) (\(n = 29\) had statistically significant higher serum IL-18 levels than those who received CS ± other immunosuppressives (\(n = 12\) (167.22 ± 56.46, 119.16 ± 53.87 pg/ml respectively, \(p = 0.016\)). However, no significant correlation was demonstrated between serum IL-18 and daily dose of prednisolone (\(r = 0.168, p = 0.294\)), azathioprine (AZA) (\(r = 0.135, p = 0.549\)), hydroxychloroquine (OHCQ) (\(r = 0.178, p = 0.623\)) cyclosporine A (CsA) (\(r = 0.113, p = 0.790\)) and number of CYC pulses (\(r = 0.032, p = 0.841\)).
4. Discussion

SLE is a complex disease driven by the activation of different lymphokine systems at different time-points, possibly explaining the heterogeneity of clinical manifestations [19]. Lupus nephritis is a major contributor to morbidity and mortality in patients with SLE and up to half of lupus patients develop LN during the course of their disease [2]. It has recently become evident that abnormal production of Th cell cytokines and chemokines is primarily involved in kidney damage of SLE. Increased Th1:Th2 (IFN-γ:IL-4) ratio was proposed to promote renal damage in SLE with predominance of Th1 cytokines in the kidneys of patients with diffuse proliferative LN [20].

IL-18 previously known as IFN-γ-inducing factor was found to be correlated with disease activity and renal damage in SLE in both human and animal investigations [8,21]. Upregulation of this proinflammatory cytokine accelerated proteinuria and caused aggravation of nephritis. Furthermore, intramuscular vaccination of young MRL/lpr mice with a cDNA encoding murine IL-18 elicited significant reductions in lymphoproliferation, renal damage and mortality [22]. On the other hand, some authors have not demonstrated significant associations between serum IL-18 and any kind of renal manifestation in SLE patients [11]. So, there is a conflict about the possible role of IL-18 in the pathogenesis of LN.

Serum IL-18 level was found to be significantly higher in SLE patients with and without LN than that in healthy controls in agreement with several studies [2,4,7,9,13,23–28]. Furthermore, the present results approved previous studies that serum level of IL-18 was significantly higher in patients with LN than that of lupus non-nephritis patients [2,9,23]. This suggests the possible role of IL-18 in the pathogenesis of SLE, in particular LN.

### Table 1  Baseline characteristics of lupus nephritis and lupus non-nephritis patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with lupus nephritis (n = 41)</th>
<th>Lupus non-nephritis patients (n = 31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Female/Male)</td>
<td>32/9</td>
<td>28/3</td>
<td>0.21</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>32.41 ± 11.57</td>
<td>36.03 ± 12.15</td>
<td>0.20</td>
</tr>
<tr>
<td>Duration of the disease (yrs)</td>
<td>4.67 ± 3.86</td>
<td>6.07 ± 6.02</td>
<td>0.23</td>
</tr>
<tr>
<td>SLEDAI score (mean ± SD)</td>
<td>24.63 ± 12.92</td>
<td>23.00 ± 9.88</td>
<td>0.56</td>
</tr>
<tr>
<td>Renal activity score (mean ± SD)</td>
<td>8.75 ± 4.95</td>
<td>34.90 ± 19.80</td>
<td>0.64</td>
</tr>
<tr>
<td>ESR 1st hour (mm/h)</td>
<td>37.37 ± 23.67</td>
<td>97.39 ± 29.74</td>
<td>0.18</td>
</tr>
<tr>
<td>C3 (mg/dl)</td>
<td>86.73 ± 36.07</td>
<td>59.28 ± 48.40</td>
<td>0.16</td>
</tr>
<tr>
<td>Anti-dsDNA titer (IU/ml)</td>
<td>79.4 2 ± 67.53</td>
<td>1.15 ± 0.50(0.6–2.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean serum creatinine (range) mg/dl</td>
<td>1.15 ± 0.50(0.6–2.7)</td>
<td>0.81 ± 0.13(0.6–1.1)</td>
<td></td>
</tr>
<tr>
<td>WHO Class of LN (n %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>5 (12.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>12 (29.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>17 (41.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>7 (17.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity index (24) (mean ± SD)</td>
<td>10.22 ± 4.11</td>
<td>29 (93.55%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronicity index(12) (mean ± SD)</td>
<td>2.54 ± 1.21</td>
<td>15.09 ± 11.62</td>
<td></td>
</tr>
<tr>
<td>Treatment with prednisone (n%)</td>
<td>41 (100%)</td>
<td>29 (93.55%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Daily dose, mg (mean ± SD)</td>
<td>25.61 ± 14.14</td>
<td>15.09 ± 11.62</td>
<td></td>
</tr>
<tr>
<td>Treatment with NSAIIDs (n%)</td>
<td>0 (0%)</td>
<td>5 (16.13%)</td>
<td></td>
</tr>
<tr>
<td>Treatment with AZA (n%)</td>
<td>25 (60.98%)</td>
<td>21 (67.74%)</td>
<td></td>
</tr>
<tr>
<td>Daily dose, mg (mean ± SD)</td>
<td>81.82 ± 22.07</td>
<td>95.24 ± 26.95</td>
<td></td>
</tr>
<tr>
<td>Treatment with OHCQ (n%)</td>
<td>10 (24.39%)</td>
<td>17 (54.84%)</td>
<td></td>
</tr>
<tr>
<td>Daily dose, mg (mean ± SD)</td>
<td>380.00 ± 113.53</td>
<td>258.82 ± 93.93</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Treatment with CsA (n%)</td>
<td>10 (24.39%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Daily dose, mg (mean ± SD)</td>
<td>75.00 ± 23.15</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>Treatment with CYC (n%)</td>
<td>29 (70.73%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Number of pulses</td>
<td>5.10 ± 3.58</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

AZA = azathioprine, OHCQ = hydroxychloroquine, CsA = cyclosporin A, CYC = cyclophosphamide.
It was found that age and sex did not influence the serum levels of IL-18 in SLE patients [7,9] consistent with our results. In addition, the present data did not find significant relations between serum IL-18 and organ involvement other than the renal system in SLE patients except for CNS involvement. It is worthy to mention that IL-18 transcript was demonstrated by RT-PCR in a variety of brain regions in mice [29]. In addition, it was demonstrated in vitro that microglia and astrocytes can produce IL-18 and its level can be up-regulated following lipopolysaccharide stimulation or treatment with INF-γ. There are also some studies that support a function for IL-18 in the onset and progression of autoimmune CNS disease [30], but its role in SLE CNS disease needs further research.

Similarly, other studies found no association of IL-18 levels with organ involvement other than renal disease, so they suggested that the high IL-18 serum titers within their SLE cohorts were primarily attributable to the occurrence of LN [2,9]. On the other hand, others did not find significant associations between serum IL-18 and any clinical manifestations of SLE including renal manifestations [10,11]. This may be related to the small number of SLE patients with renal disease in their studies.

The present study showed a significant correlation between serum IL-18 and SLE disease activity measured by SLEDAI in all 72 SLE patients. Upon subgroup analysis, serum IL-18 correlated significantly with SLEDAI score in patients with LN but not in lupus non-nephritis patients. This further indicates that IL-18 played an inflammatory role in glomerulonephritis of SLE patients. This result is in concordance with that of Wong et al. [23] and in partial agreement with another study that demonstrated a significant correlation of plasma IL-18 concentration with SLEDAI score in both renal and non-renal SLE groups [13]. Like minded, it was demonstrated that the mean IL-18 level at the active stage (SLEDAI >6) was significantly higher than that at the stable stage after treatment suggesting that IL-18 might contribute to the flare of the disease [24].

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Correlation between serum level of IL-18 and laboratory tests for assessment of renal function.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IL-18 (pg/ml) in patients with LN (n = 41)</td>
<td>Serum creatinine (mg/dl)</td>
</tr>
<tr>
<td>R</td>
<td>0.504</td>
</tr>
<tr>
<td>P</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Pearson correlation co-efficiency test–P is significant if ≤0.05.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Comparison between the serum levels of IL-18 in different classes of lupus nephritis patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum IL-18 (pg/ml) in LN patients (n = 41) mean ± SD</td>
<td>P</td>
</tr>
<tr>
<td>Class 2 (n = 5)</td>
<td>121.90 ± 60.44</td>
</tr>
<tr>
<td>Class 3 (n = 12)</td>
<td>152.53 ± 46.01</td>
</tr>
<tr>
<td>Class 4 (n = 17)</td>
<td>167.01 ± 67.41</td>
</tr>
<tr>
<td>Class 5 (n = 7)</td>
<td>107.34 ± 60.66</td>
</tr>
</tbody>
</table>

One way ANOVA test is used.
We have found a significant correlation between serum IL-18 and anti-dsDNA titer in all SLE patients and in the group of LN. Moreover, significant negative correlations between serum IL-18 and serum C3 and C4 were demonstrated in patients with LN while no significant correlation was found with ESR. In another study, serum IL-18 correlated significantly with anti ds-DNA titer in SLE patients during the active stage, while not significantly correlated with the other laboratory parameters including ESR, C3 and C4 [24]. Hu and coworkers did not also find any significant correlation between the serum IL-18 level in LN patients and ESR or C3 [27]. This inconsistency with our results may be due to lower disease activity than that of our patients.

The association between serum levels of IL-18 and WHO pathological classes of LN was further investigated in this study. It was found that class IV patients had the highest serum IL-18 levels followed by class III then class II and the lowest were for class V. However, the difference of IL-18 levels among the pathological classes was not statistically significant as reported previously [27]. Moreover, Shimizu and coworkers recognized a significant increase in the serum levels of IL-18 in LN Classes II, III and IV versus control however, the serum level stayed within the non-significant range in Class V [28]. Furthermore, in the study by Chen and colleagues, significant higher levels of serum IL-18 were observed in LN patients with WHO class IV than in those with class III, while there were no significant differences in the serum IL-18 levels between class III and class V or between class IV and class V [4]. On the other hand, highest titers of serum IL-18 were demonstrated in patients with classes IV and V followed by class III and class II [2,9]. Interestingly, a significant correlation between AI (but not histological C1) and serum IL-18 in LN patients was recognized in this study. This result indicates that the serum level of IL-18 may be related to the degree of activity of LN within each class rather than the WHO pathological classification of the disease. Furthermore, the level of ongoing histological activity may not be correlated with the cumulative histological injury [28]. Hu and coworkers are partially in agreement with our results as they did not find any significant correlation between serum IL-18 and both AI and CI of renal biopsy in patients with LN [27]. However, a close positive correlation was found between IL-18 glomerular expression and IL-18 in urine of LN patients with AI and not with CI [31–33].

A significant correlation between serum IL-18 level and the SLICC renal activity score was demonstrated. Additionally, serum IL-18 of patients with LN showed a significant correlation with serum creatinine, 24 h urinary protein and P/C ratio. These results verify that measurement of the serum level of IL-18 can reflect the activity of LN supporting the other laboratory tests for assessment of renal function. Consistent with our results, a significant correlation was demonstrated between serum level of IL-18 and urinary microalbumin [9], and serum creatinine [25] in SLE patients. On the other hand, other studies revealed that there were no significant correlations between serum IL-18 levels either with 24-h urine protein levels [27], or serum creatinine levels [7] in SLE patients. This discrepancy with our results may stem from different sizes of the cohort studied, ethnic origin of the patients, and from difference in the definitions of renal involvement.

Contrary to usual expectation, it was found that patients with LN who received CS ± CYC had statistically significant higher serum IL-18 levels than those who received CS ± other immunosuppressives. This result may be due to higher activity in our patients with LN receiving CYC. No significant correlation was also demonstrated between serum IL-18 and daily dose of prednisolone, AZA, OHCQ, CsA and number of CYC pulses in consistent with the results of Wong et al. [23]. Moreover, Robak et al. reported that the serum IL-18 level was not correlated to the use of drugs as immune inhibitors [10] suggesting that their elevated concentrations are connected with the disease itself and not with the effect of treatment. Other authors’ observations of the effect of SLE treatment on IL-18 concentrations are divergent as they found a positive correlation existing between IL-18 concentration and glucocorticoid dose taken by the patients at examination [25]. This correlation could not be explained whether it was a direct effect of CS treatment or simply a reflection of the increased SLEDAI justifying a higher prednisolone dose. Contrary to our results, two recent studies revealed that patients with LN treated with prednisone in combination with CYC pulse therapy have significantly lower IL-18 levels than those treated without CYC, but still higher than control, and other immunosuppressive agents such as high dose CS, AZA and OHCQ tended to lower this cytokine though the difference was not significant [17,27].

In conclusion, IL-18 appears to have a pathogenic role in the development of SLE, and plays a crucial role in triggering inflammation in LN. Serum IL-18 levels could be a useful biomarker to assess the activity of renal disease in SLE. However, further studies are required to understand the exact mechanism by which IL-18 contributes to the pathogenesis and activation of LN.

Conflict of Interest

The authors declare that they have no conflict of interest.

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References

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