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Proinflammatory interferon-gamma - inducing monokines (interleukin-12, interleukin-18, interleukin-15) - serum profile in patients with systemic lupus erythematosus

Abstract

Concentrations of three interferon-gamma - inducing monokines, IL-12, IL-18 and IL-15, were investigated in the serum of 60 patients with systemic lupus erythematosus (SLE) and 20 healthy subjects. IL-12 and IL-18 were detectable in the serum of all patients with SLE and in all healthy controls. The level of IL-12

was significantly higher in SLE patients (median 264.9 pg/ml) than in the control group (median 163.6 pg/ml, p < 0.02). Similar differences were observed in the level of IL-18 (median values 602.2 pg/ml and 252.7 pg/ml, respectively, p < 0.001). Correlations between serum levels of IL-12 and IL-18 and SLE activity were not statistically significant (p > 0.05). We found a significant, positive correlation between IL-12 and IL-18 (rhô = 0.419, p < 0.001) in SLE patients. The level of IL-18 was higher in the SLE patients with antinuclear antibodies (ANA) (median 660.0 pg/ml) than in ANA-negative patients (median 326.5 pg/ml, p < 0.03), as well as in patients with immunoglobulin deposits at the dermal-epidermal junction (median 746.0 pg/ml and 444.0 pg/ml respectively, p < 0.04). The level of IL-12 was also higher in patients with skin immunoglobulin deposits (328.9 pg/ml) than those without this phenomenon (257.0 pg/ml, p < 0.05). The levels of both cytokines in the patients treated with immunosuppressive drugs and those patients not treated were similar. The serum levels of IL-15 were low and not significant both in SLE patients (median 2.9 pg/ml), and in healthy controls (median 1.6 pg/ml). In conclusion, serum levels of IL-12 and IL-18 are higher in SLE patients than in healthy controls which may indicate a role in the disease pathogenesis. However, they do not correlate with disease activity and seem to be unresponsive to immunosuppressive treatment.

Full text

INTRODUCTION

In recent years, several novel proinflammatory cytokines with possible roles in SLE pathogenesis have been discovered. Among them, IL-12, IL-18 and IL-15 levels have been found to be elevated in the serum and/or plasma from SLE patients [1-4]. However, the association between these cytokines levels and disease activity as well as particular clinical and laboratory symptoms of SLE, have not been so far fully investigated.

IL-12 is a pleiotropic cytokine which mediates several biological activities of human T and natural killer (NK) cells, including induction of IFN-gamma production, enhancement of cell-medicated cytotoxicity and co-mitogenic effects on resting T-cells [5]. IL-12 can induce the production of IL-18 and has a synergistic effect with IL-18 on the activation of NK cells and cytotoxic T lymphocytes (CTL) [6].

IL-15 is also a pleiotropic cytokine, derived from several cell types including macrophages and fibroblasts [6-8]. This cytokine was found to share many biological activities with IL-2, although it shows no homology with IL-2. It has been shown that IL-15 stimulated proliferation of cytotoxic T cells, regulates survival of NK cells and inhibits apoptosis [6-8]. IL-15 not only shares biological activities with IL-2 but also uses the same beta- and gamma-receptor subunits [9]. As a consequence, the influence of IL-2 and IL-15 on immunological system may be similar.

IL-18 was initially described as IFN-gamma-inducing factor [10]. This cytokine has structural homology with IL-1, sharing some common signalling pathways and biologically similar inflammatory functions [11]. Moreover, similarly to IL-1, IL-18 requires cleavage at its aspartic acid residue by IL-1-converting enzyme to become the mature, active protein. The common attribute of IL-12, IL-15 and IL-18 is their production by activated macrophages. Moreover, these three monokines are inducers of IFN-gamma production [11-14]. Taking into account the fact that IFN-gamma is a major effector molecule in SLE [15] the investigation of IL-12, IL-15 and IL-18 in the same patients with this disease seems to be warranted.

In the present study, we evaluated the serum levels of selected proinflammatory cytokines (IL-12, IL-15, IL-18) in patients with SLE. We also correlated the serum concentrations of these proteins with the disease activity and some particular symptoms of the disease.

PATIENTS AND METHODS

The study involved 60 patients with SLE (56 females and 4 males). Their mean age was 41 years (range 17-76 years). The diagnosis of SLE was based on the revised criteria of the American Rheumatism Association [16]. The clinical and laboratory features of SLE patients are presented in *Table 1*. The mean duration of their disease was 62 months (range 6 months-22 years). At the time of the study, only fourteen patients had been treated with prednisone at doses ranging between 5 and 30 mg/day, and five of them with azathioprine 50-100 mg/day or cyclophosphamide 100 mg/day. On the day of blood sampling, each patient's history was recorded and a physical examination was performed. Disease activity was scored according to the method described by Liang *et al*. [17]. The system of Systemic Lupus Activity Measure (SLAM) includes 24 clinical manifestations and eight laboratory parameters. The maximum score in this

system is 84 points. In the present study in our group of patients the number of points ranged from 9 to 27. We assumed the score of 0-15 points for inactive disease and a score of over 15 points for active disease. Our cohort of patients included 32 active and 28 inactive patients. The control group consisted of 20 healthy individuals, 18 women and 2 men, aged from 18 to 65 years (median 38 years). The patients with SLE and controls showed neither clinical signs of infection nor neoplastic disease, and received neither antibiotics, nor nonsteroid anti-inflammatory drugs for at least 4 weeks prior to blood donation. This project was performed in accordance with the Helsinki Declaration and was approved by the local Ethics Committee. Informed consent was obtained from all the patients.

Laboratory tests

On the day of blood sampling for cytokine determination the following laboratory parameters were analysed: complete blood cell count, erythrocyte sedimentation rate (ESR), partial thromboplastin time (PTT), GOT, GPT, urinalysis, urea, creatinine, fibrinogen, bilirubin, serum IgG, IgM, IgA and complement (C3, C4) levels. Antinuclear antibodies (ANA) were estimated by indirect immunofluorescence method (IIF) on HEp-2 substrate and on *Crithidium lucilliae* substrate for anti-dsDNA detection. Double immunodiffusion was used for Sm, Ro/SS-A, La/SS-B, RNP antibody identification. Immunoglobulin deposits at the dermal-epidermal junction (Lupus band test-LBT) were also determined.

Cytokine determination

Venous blood collected at the time of clinical assessment in pyrogen-free tubes, was allowed to clot at 4° C for 1h and centrifuged at 2,000 g for 10 min. The sera obtained were divided into aliquots, placed into separate vials and stored at -25° C until assayed for cytokines. The cytokine serum levels were assessed by commercially available, enzyme-linked assay (ELISA) kits in accordance with the manufacturer's instructions and analysed with an ELISA reader at 492 nanometers. The IL-15 kit was obtained from R&D Systems Inc, Minneapolis, USA, the IL-12 kit from Endogen. Inc. Woburn Ma, USA and the IL-18 kit from MBL Medical & Biological Laboratories Co., LTD, Naka-ku, Nagoya, Japan. Assay sensitivity was 2 pg/ml for IL-15, 5 pg/ml for IL-12 and 12,5 pg/ml for IL-18. The procedure has been described in detail elsewhere [18].

Statistical analysis

For the statistical analysis of the data, the range of variables is given (min-max). Mean arithmetic value (x), median (Me) and standard deviation (SD) have also been calculated. The Shapiro-Wilk's test was used to evaluate the distribution. The comparison of variables values in two groups was performed depending on the distribution of features of the Mann-Whitney test, or the test for two means for independent samples or Cochran-Cox test. The correlation between features was evaluated using the Spearman rank coefficient rhô. Comparisons and correlations were considered significant when $p < 0.05$.

RESULTS AND DISCUSSION

IL-12 and IL-18 were detectable in the serum of all 60 patients with SLE and in all persons from the control group. The level of IL-12 was higher in SLE patients (median 264.9 pg/ml) than in the controls (median 163.6 pg/ml) ($p < 0.02$) *(Table 2)*. No difference in IL-12 serum concentrations in inactive SLE compared with active SLE was observed (median 231.6 pg/ml and 276.1 pg/ml, respectively), ($p > 0.05$).

The serum level of IL-18 was also significantly higher in the whole SLE group (median 602.2 pg/ml) than in controls (median 252.7 pg/ml) ($p < 0.001$). However, there was no statistically significant difference between active SLE (median 569.7 pg/ml) and inactive stage of the disease (median 624.7 pg/ml) ($p > 0.05$).

These results are in agreement with other authors' observations [2, 4]. Wong *et al*. [2], estimating IL-12 and IL-18 concentrations in the plasma of 36 SLE patients, found higher levels of both cytokines in the patient group compared to the controls. Higher concentrations of IL-12 in SLE patients sera were also observed by Tokano *et al*. [19].

In contrast to our results Wong *et al*. found a significant positive correlation between IL-18 concentration and SLE activity, estimated according to the SLEDAI score, as well as between the IL-18/IL-4 concentration ratio and disease activity [1, 2]. However, in their study the correlation between IL-12/IL-4 concentration ratio and SLE activity was not statistically significant.

The differences between the lack of correlation of IL-18 concentration and SLE activity in our study and the presence of such a correlation in the Wong *et al*. [1] study might be the result of the fact that Wong *et al*. measured the cytokine concentration in plasma, but in our study it was measured in serum. However, it seems that using different methods for evaluating SLE activity cannot significantly influence the results as both scoring systems give comparable results and a good correlation [20].

Our study showed a strong positive correlation between IL-12 and IL-18 serum concentrations in SLE patients ($r = 0.419$; $p < 0.001$) but not in the control group ($r = 0.018$, $p > 0.05$) (Figure 1).

Correlations between plasma concentrations of these cytokines in SLE patients were also analysed by Wong *et al*. [1] although, contrary to our results, they found no statistically significant correlation ($r = 0.168$, $r = 0.3$). The correlations between IL-18 and IL-12 concentrations could be explained by the results of laboratory experiments. IL-12 induces IL-18 production and they both synergistically activate NK cells and cytotoxic lymphocytes T [6, 21]. One may speculate that higher concentration of IL-12 in SLE patients stimulates IL-18 release which results in increased serum concentration of both cytokines. As it was shown by other studies, combination of IL-12 and IL-18 gives optimal stimulation for IFN-gamma production by NK cells, whereas combined usage of IL-15 and IL-12 stimulates IL-10 production more than IL-18 and IL-12 [6].

Our experiments showed a significant difference in IL-12 and IL-18 concentrations depending on the presence of specific clinical symptoms and laboratory results. The level of IL-18 was higher in patients with antinuclear antibodies (median 660.0 pg/ml) than in ANA-negative patients (median 326.5 pg/ml) ($p < 0.03$). Althought, the presence of anti-dsDNA antibodies was connected with higher IL-12, IL-18, we did not find any statistically significant correlation between the specific type of antibodies and the cytokines levels analysed, but higher concentrations of IL-18 were observed in patients with (median 746.0 pg/ml) than without (444.0 pg/ml) immunoglobulin deposits at the dermal-epidermal junction ($p < 0.04$). Similarly, the level of IL-12 was also higher (median 328.9 pg/ml) in the group of SLE patients with positive LBT, than in patients with negative LBT (median 257.4 pg/ml) ($p < 0.05$).

We also tried to compare the levels of IL-12 and IL-18 with the presence of skin lesions, neurological symptoms, reticuloendothelial system and renal involvement, arthritis, other laboratory abnormalities, and therapy administered. It is worth pointing out that all of the differences between the above mentioned parameters and cytokines levels examined were not statistically significant.

Our observations are in agreement with the experiments conducted on MRL/lpr mice, which is the animal model for spontaneous lupus-like autoimmune disease. Under the influence of exogenous IL-18, the symptoms of vasculitis, proteinuria, the presence of immunoglobulins in skin and the higher production of anti-dsDNA antibodies and proinflammatory monokines developed in MRL/lpr mice [22]. Moreover, it was shown that in MRL/lpr mice, NK cells and lymphocytes T over-express IL-18 receptor (IL-18R) and are hypersensitive to IL-18 [23]. It was also shown that under specific conditions, IL-12 up-regulates IL-18 receptor expression [24], and that using anti-IL-12 antibodies in mice may slow down the progression of the disease [25]. Our clinical observations are in line with the results of laboratory experiments, and indicate that IL-18 and IL-12 may play a role in the pathogenesis of SLE. Despite the fact that IFN-gamma concentrations in serum and its correlation with the monokines were not estimated in the current study, high levels of IFN-gamma in SLE patients and MRL/lpr mice have been observed by other authors [16, 17]. Moreover, it was proved that IFN-gamma is essential for the development of lupus-like disease and lymphoaccumulation in MRL lpr mice [28].

There was no difference in the monokines concentrations between treated and untreated patients (data not shown). Other authors' observations of the effect of SLE treatment on IL-12 and IL-18 concentrations are divergent. Wong *et al.* found a statistically significant positive correlation between IL-18 concentrations and the dose of prednisone ($r = 0.55$, $p < 0.01$), but they did not find any difference among SLE patients treated with azathioprine, hydroxychloroquine or cyclosporine A [2]. The lack of any treatment effect on IL-12 and IL-18 levels, suggests that their elevated concentrations are connected with the disease itself and not with the effect of the treatment.

The serum concentrations of IL-15 were higher in SLE patients (median 2.9 pg/ml) than in the control group (median 1.6 pg/ml) ($p < 0.003$). In two other studies conducted on SLE patients, IL-15 serum levels were also higher than in the control group [4, 13]. Because IL-15 serum concentrations in our study were

below the detection limit (2 pg/ml) in 20 (33%) SLE patients and in 13 (60%) healthy persons we did not analyse the relationship between this cytokine and clinical or laboratory symptoms.

CONCLUSION

In conclusion, The statistically significant, elevated levels of IL-12 and IL-18 in patients examined indicate their possible role in the pathogenesis of SLE. As the monokine levels do not correlate with the disease activity and do not depend on the any treatment administered, it seems that they may not be considered as a useful parameter in disease activity assessment.

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Figures

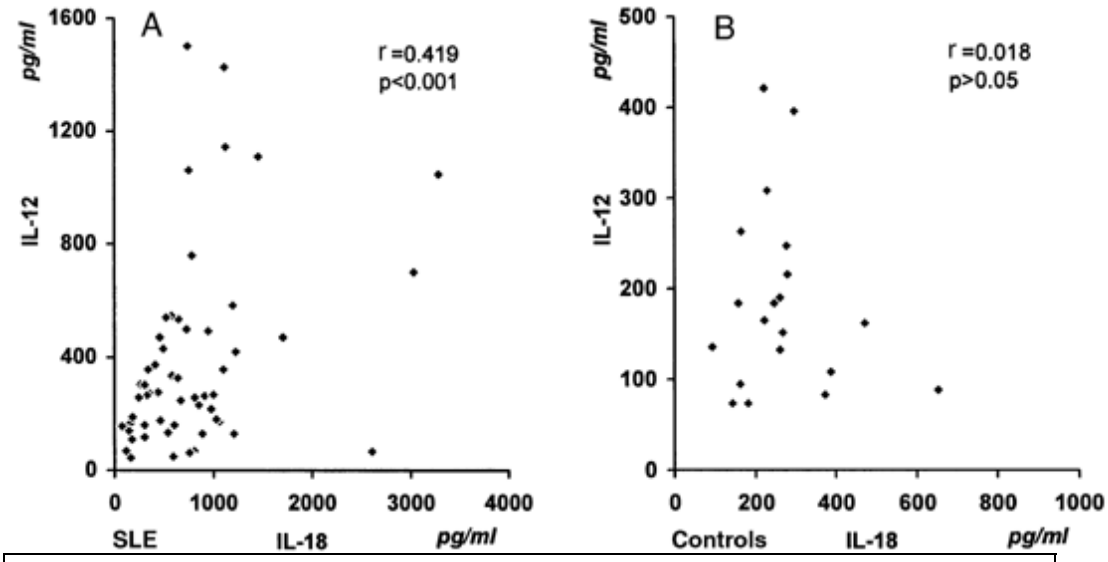

Figure 1

Correlations between IL-18 and IL-12 serum concentrations in patients with SLE (A) and healthy controls (B).

Table 1
Clinical material and parameters analysed in SLE patients

Clinical/laboratory features	Number of patients	%
Total	60	100.0
Age (years)		
median (range)	41 (17-76)	
Sex (male/female)	4/56	8.3%/91.7
Active/Inactive disease	32/28	53.3%/ 46.7
Fever	14	23.3
Arthritis	55	91.7
Skin lesions	30	50.0
Reticuloendothelial system involvement	36	60.0
Renal disorder (creatinine > 1.3 mg/dl, proteinuria)	57	95.0
Neurological symptoms	37	61.7
Antinuclear antibodies (≥ 160)	50	83.3
LBT	35	58.3
Anemia (Hb < 12 g/dl)	30	50.0
Leukopenia (WBC < 3.5 x 10⁹/L)	19	31.7
Thrombocytopenia (platelets < 150 x 10⁹/L)	13	21.7
C reactive protein (> 4.7 mg/L)	16	26.7
Raised ESR (> 25 mm/h)	24	40.0
Immunosuppressive treatment (steroids, cytotoxic agents)	14	23.3

Table 2
Serum levels of IL-12 and IL-18 in patients with SLE and the control group (values in pg/ml)

Factor	All SLE n = 60 (a)	Active SLE n = 32 (b)	Inactive SLE n = 28 (c)	Control group n = 20 (d)	Statistical comparisons	
IL-12						
$\bar{x} \pm SD$	372.8 ± 336.3	381.7 ± 301.2	231.6 ± 376.7	184.1 ± 100.5	(a)-(d)	p < 0.02
Median	264.9	276.1	231.6	163.6	(b)-(c)	p > 0.05
Range	(44.5- 1,501.2)	(48.2- 1, 144.2)	(44.5- 1,501.2)	(73.3-421.3)	(b)-(d)	p < 0.02
					(c)-(d)	p > 0.05
IL-18						
$\bar{x} \pm SD$	744.4 ± 638.0	858.2 ±818.3	614.3 ± 296.1	267.3 ±127.8	(a)-(d)	p < 0.001
Median	602.2	569.7	624.7	252.7	(b)-(c)	p > 0.05
Range	(79.5-3,283.5)	(79.5-3,283.5)	(161.5- 1, 114.0)	(93.0-653.0)	(b)-(d)	p < 0.001
					(c)-(d)	p < 0.001

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Proinflammatory interferon-gamma - inducing monokines (interleukin-12, interleukin-18, interleukin-15) - serum profile in patients with systemic lupus erythematosus

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SLE, Interferon gamma, IL-12, IL-15, IL-18, disease activity.

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