ORIGINAL PAPER

Cytokine panel and histopathological aspects in the systemic lupus erythematosus

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Abstract

The systemic lupus erythematosus (SLE), a systemic autoimmune disorder with a multifactorial etiology, is characterized by the presence of autoantigens in some organs and tissues that induce the development of some antibodies with extended binding and with various specificities. The presence of antibodies is accompanied by disbalances in the immune cellular response, including alterations in the production of some cytokines. Cytokines, quite a heterogeneous group of protein molecules produced in small quantities by certain specifically stimulated cells, have the capacity to maintain the communication between different cell populations that participate in the immune response (messengers of the immune system), thus modeling a defense function. *Objectives*: The purpose of the study is to estimate the seric levels of some proinflammatory, anti-inflammatory and immunomodulating cytokines in patients diagnosed with SLE, as well as some correlations between the seric levels of these cytokines and the histopathological aspects. *Material and Methods*: There were included in the study 35 patients diagnosed with SLE (active/remission stage of the disorder), in whom there were determined, before administering the treatment with the immunoenzymatic technique ELISA, the seric level of the following cytokines: interleukins (IL) IL-2, IL-6, IL-8, IL-10, and the tumor necrosis factor-alpha (TNF-alpha). The obtained results in the patients were compared to those observed in a control group, made up of 35 healthy subjects. *Results*: The IL-2 production of T-lymphocytes was a deficient one (low seric levels in the majority of the patients), while cytokines IL-6, IL-8 and TNF-alpha showed high seric levels. IL-10 plays a very important role in the SLE pathogeny, through the high seric levels, and it may be involved, as a predictive biological marker, in the quantification of the activity degree of the disorder. *Conclusions*: SLE represents an autoimmune disorder, characterized, among others, by a disbalance in the cytokine network. Signaling and regulating abnormalities of B-lymphocytes by cytokines are responsible of the excessive production of antibodies. IL-6 and IL-10 were proved to be key factors in the intensification of the inflammation and regulation of B-lymphocytes activity, by their polyclonal activation. Alongside TNF-alpha, they play an important part in the development of severe dermo-epidermal alterations.

Keywords: systemic lupus erythematosus, IL-6, IL-10, TNF-alpha.

⬚ Introduction

The systemic lupus erythematosus (SLE) represents the most important autoimmune disorder in which the suffering may specifically affect certain organs and/or may have systemic symptomatic effects. It is characterized by an endless source of antibodies with various specificities [anti-nuclear: anti-RNA, anti-DNA, anti-histone; anti-ribosomal; anti-collagenous; anti-IgG (rheumatoid factor); anti-leukocyte (ANCA); anti-phospholipids and extended binding. These autoantibodies appear consecutively with the presence of dispersed autoantigens in the whole body and they consist of nucleoproteins (ENA antigens), (mono- and double-chained) DNA, components of the conjunctive tissue, immunoglobulins, coagulation factors. The destructive mechanisms that are produced in this inflammatory chronic disorder are mainly due to the hypersensitivity phenomena type III (immune complex disorder) [1].

SLE frequently appears in women (90% of cases) related to a certain haplotype (HLA-A1, -B8, -DR3). The disorder recognizes as the primary triggering factors the bacterial infections (*Streptococcus*) and viral infections (rubella, roseola viruses, epidemic parotiditis), the hormonal, toxic influences, (chemical factors-drugs and nutritional factors-hyperlipidic and hyper-caloric diet), the stress, the UV radiations [2].

The symptoms develop in the majority of the patients as a triad made up of skin lesions, joint syndrome and glomerulonephritis. To these, there are also added numerous other symptoms of the affected organs, thus forming a polymorphous clinical aspect. The evolution of the disorder is a chronic and progressive one, leading to serious renal, pulmonary or hepatic lesions.

Within the SLE pathogeny, there are involved auto-

immunity phenomena given by autoantigen–autoantibody immune complexes at a renal level, thus leading to lupic nephritis, or on the walls of blood vessels, generating disseminated vasculitis. To these, there are also added disturbances of the cellular immune response: T-cytolytic cells deficit (Tc), reduction of cytotoxic NK activity, alterations in the production of some cytokines.

Cytokines represent a heterogeneous group of protein molecules produced by certain specifically stimulated (lymphoid and non-lymphoid) cells. The biological (proinflammatory, hematopoietic, immunomodulatory, chemoattractant) effects of cytokines are based on the role of messengers of the immune system, thus acting through specific receptors and distinct intracellular signaling ways [3]. They play a central part in the physiological reactions of cellular growth and differentiation, of tissular repairing and remodeling, and in the inflammatory and immune reactions, as well. Within the inflammatory response of SLE there is established a real "hierarchy" between the involved cytokines regarding the moment of production and the intensity of biological effects, the cytokines production stimulating or, on the contrary, blocking the production of other cytokines [4].

There are over 50 molecular species of cytokines: over 20 interferons, 15 chemokines, numerous cellular growth factors and 18 interleukins. The latter are produced by B- and T-lymphocytes, macrophages, stromal cells from the hematogeneous bone marrow, endothelial cells, as well as many other cell types. They are active on a great variety of cells, but mainly on the leukocytes participating in the immune response, having the capacity to maintain the communication among them, thus modeling the defense function [5, 6].

In SLE, the excessive production of antibodies is considered to be definitory, but the mechanisms for its development are not completely elucidated. Taking into consideration that cytokines play a very important role in the inflammatory response, and that multiple cytokines-mediated deficiencies are present in individuals with SLE, a deficiency in the immune regulation of B-lymphocytes by cytokines could be considered a possible advocate in the pathogeny of the disorder [3, 7].

Lots of authors consider that the B-lymphocytes hyperactivity is a secondary one and seems to be, on the one hand, determined and closely related to the abnormalities of B-lymphocytes signaling and regulation given by cytokines [8], and, on the other hand, to the disturbances of the function of T-lymphocytes, which are incapable of inhibiting both B-lymphocytes proliferation and the T-lymphocytes differentiation and activation, as well. T-lymphocytes are mainly deficient in the production of IL-2, the main cytokine that assures the inter-lymphocytary relationship. There are arguments that plead in favor of the T-lymphocytes hyperactivity in SLE, but there are also elements in favor of the activation of other lymphocytary populations. Thus, B-lymphocytes secret a large series of cytokines those act as growth factors for other B-lymphocytes, assuring the evolution of the process.

In conclusion, both genetical and environmental factors are involved in the SLE etiopathogenesis, thus leading to complex immune alterations. The most immune abnormalities encountered in SLE patients regard the inter-lymphocytary relationships. Even if B-lymphocytes hyperactivity is a constant one, thus determining hypergammaglobulinemia and synthesis of antibodies, the debut of alterations seems to be more at the level of T-lymphocytes, by losing the self-regulation memory, a fact that determines the proliferation both of T-helper lymphocytary clones and of B-lymphocytes that synthesize antibodies. Once these elements appear, the distortion of homeostatic mechanisms supports and maintains the B-lymphocytes hyperactivity. The damage itself is produced through circulant immune complexes and antibodies, as well [9, 10].

Objectives

Starting from the fact that interleukins are glycoproteins or soluble proteins that initiate, maintain, amplify or block the activation, growth, multiplication and the performing functions of the immune systems, the purpose of our study is to estimate the seric levels of some proinflammatory, anti-inflammatory and immunomodulatory cytokines and to establish subsequent correlations with the histopathological aspects in the SLE patients.

⊟ Material and Methods

There were included in the study 35 patients diagnosed with SLE, in an active or remission stage of the disorder, coming from various healthcare units in Craiova (Emergency County Hospital, Railroad Hospital, and "Filantropia" Hospital) or from the ambulatory section, between 2007–2009. The study group was constituted of adults, aged over 18-year-old, 32 women and three men (a ratio of 11:1). By the ELISA immunoenzymatic technique, there was determined the seric level of the following cytokines: interleukins (IL) IL-2, IL-6, IL-8, IL-10, and the tumor necrosis factor-alpha (TNF-α). In the cases of active stage of the disorder, the determination had been done before the performance of any immunosupressive treatment. There were used the following kits of human interleukins: h-Interleukin-2 Roche Diagnostics GmbH; PeliKine™ for IL-6 and TNF-α; Milenia Biotec GmbH for IL-8 and IL-10.

The obtained results in the patients were compared to those observed in a witness (control) group, made up of 35 healthy subjects, the SLE patients' relatives or partners. In these individuals, the average seric TNF-α values were of 7.87 pg/mL, IL-6 of 7.11 pg/mL, IL-8 of 15.68 pg/mL, and IL-10 of 12.50 pg/mL.

Statistics

The description of categorial data (frequency, average, and standard deviation), the differences between group means (Student *t*-test), the linear correlation and regression test, *chi*-square test, were performed with the following program packages: SPSS *v.* 14.0 Windows, EpiInfo *v.* 3.3.2 and Microsoft Excel. Correlations and comparisons of data were considered statistically significant at $p < 0.05$.

⊟ Results

The IL-2 production of T-lymphocytes is a deficient

one (Table 1, Figure 1) in the majority of the SLE cases (except for five cases where there were determined high seric levels), the study group average being even lower than that of the witness group.

Proinflammatory cytokines (IL-6, IL-8, TNF-α) showed high seric levels with strong effects in the proliferation and differentiation of B-lymphocytes (Table 1).

These high concentrations may be responsible for the characteristic hyperactivation of B-lymphocytes and for the production of antibodies in this autoimmune disorder [11]. The IL-10 production is high in SLE patients, this increase being among the factors causing the immune disturbances in this disorder [12].

Table 1 – *Comparison between the averages of witness group and study group in all five parameters*

	Witness group			Study group			p
	No. of cases	Average [pg/mL]	Standard deviation	No. of cases	Average [pg/ml]	Standard deviation	
IL-2	35	23.4	11.854	35	22.59	26.41	0.869 (NS)
IL-6	35	7.11	3.232	35	123.71	81.783	<<0.05 (VHS)
IL-8	35	15.68	7.203	35	76.97	59.208	<<0.05 (VHS)
TNF-α	35	7.87	3.49	35	183.81	135.76	<<0.05 (VHS)
IL-10	35	12.5	6.317	35	122.73	90.62	<<0.05 (VHS)

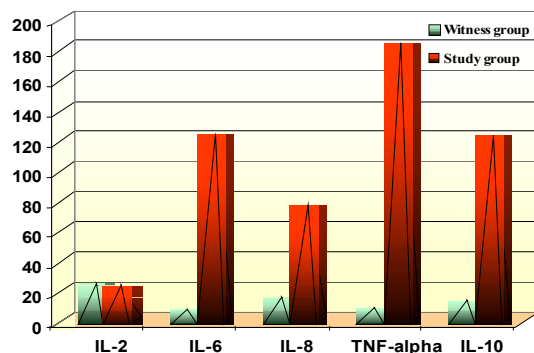NS – no significant; VHS – very highly significant.

Figure 1 – *Comparison between the averages of witness group and study group in all five parameters.*

Regarding the correlation rates among the five parameters (IL-2, IL-6, IL-8, TNF-α and IL-10) involved in the study, both in the witness group and the study one as well, we may conclude the following:

In the witness group (Table 2), the correlations among the five parameters are more insignificant, except for IL-2, IL-10 and TNF-α, which have a slight correlation tendency.

In the study group (Table 3), correlations are more significant, especially regarding the IL-10 pairs with other cytokines, except for the IL-2–IL-8 pair, which

does not correlate at all. This fact is due to the alterations induced by SLE. The IL-6, IL-8 and TNF-α parameters have the tendency to significantly correlate, thus in SLE they have high values in comparison to the witness group, also showing the tendency that high values to be manifested primarily in the same patients.

**Table 2** – *Correlation rates among the five parameters in the witness group*

	IL-2	IL-6	IL-8	TNF-α
IL-6	-0.09164	1	–	–
IL-8	0.012145	-0.00104	1	–
TNF-α	0.20531	-0.10808	0.042448	1
IL-10	0.229192	0.165458	0.080304	0.262462

Table 3 – *Correlation rates among the five parameters in the study group*

	IL-10	IL-2	IL-6	IL-8
IL-2	0.615522	1	–	–
IL-6	0.580073	0.37198	1	–
IL-8	0.414599	-0.11964	0.241263	1
TNF-α	0.505309	0.352145	0.324418	0.355284

In Figure 2, there are estimated the correlations between the seric levels of IL-10 and other cytokines (IL-2, IL-6, IL-8 and TNF-α) in the study group.

Figure 2 – *Estimation of the correlation between the seric levels of various cytokines.*
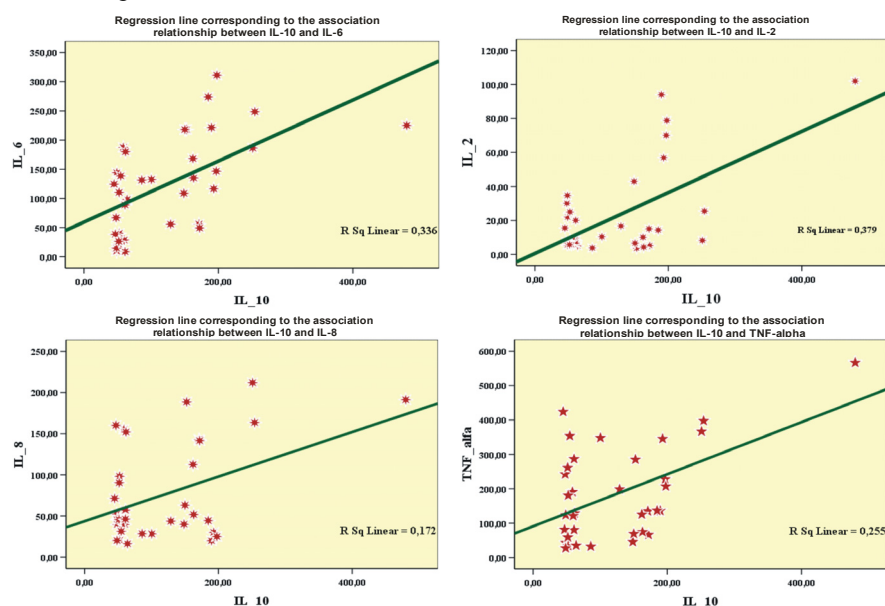
There may be noticed from Table 4 that the average of correlations between each parameter with all the other parameters is generally less significant in the witness group and higher in the study group, regarding all five parameters. The highest value is noticed in IL-10, being thus influenced in SLE, meaning that the average value of the study group, less significant than the one in the witness group, is accompanied by the tendency to have the IL-10 alterations to be accompanied by alterations of the other parameters in the same patients (Figure 3).

In a number of five patients, there were established high seric levels of IL-2, simultaneously with lower seric concentrations of IL-10 (Table 5, Figure 4).

Table 4 – *Average correlation of each parameter with the other parameters in the witness and study groups*

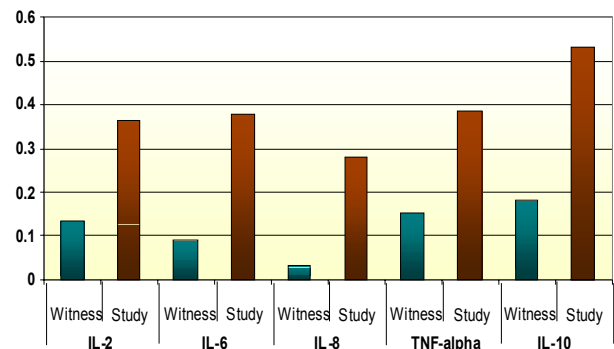|	Group	Average correlation
IL-2	*Witness*	0.134571
	Study	0.364822
IL-6	*Witness*	0.091552
	Study	0.379433
IL-8	*Witness*	0.033984
	Study	0.282696
TNF-α	*Witness*	0.154574
	Study	0.384289
IL-10	*Witness*	0.184354
	Study	0.528876

Figure 3 – *Average correlation of each parameter with the other parameters in the witness and study groups.*

Table 5 – *Comparison between the subgroup of five patients and the rest of the patients within the study group*

	Witness subgroup			Study subgroup			p
	No. of cases	*Average [pg/ml]*	*Standard deviation*	*No. of cases*	*Average [pg/ml]*	*Standard deviation*	
IL-2	30	21.95	28.46	5	26.40	6.01	0.453 (NS)
IL-6	30	135.36	80.16	5	53.80	56.01	0.0261 (S)
IL-8	30	82.63	62.05	5	43.00	14.16	0.00481 (S)
TNF-α	30	190.17	139.61	5	145.62	115.02	0.4672 (NS)
IL-10	30	134.56	92.80	5	51.74	5.47	<<0.05 (VHS)

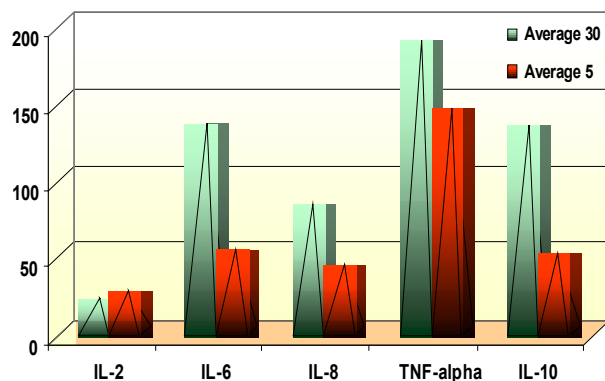NS – no significant; S – significant; VHS – very highly significant.

Figure 4 – *Comparison between the subgroup of five patients and the rest of the patients within the study group.*

Histopathologically speaking, 28 patients from the study group (80%) presented skin alterations and 12 of them showed severe dermo-epidermal alterations (disappearance of epidermal inter-papillary buds, horizontalization of dermo-epidermal junction, atrophy and even disappearance of pilosebaceous follicles).

At the level of the epidermis, there appears a hyperkeratosis with orthokeratosis, sometimes organized as corneous invaginations and in the sudoral pores. Similar aspects may also appear at the level of transversally sectioned pilous follicles in the dermis (Figure 5).

The Malpighian layer undergoes a partial atrophy that contrasts with the thickening of the corneous layer, but there may also be a certain degree of acanthosis alternating with the mucous body atrophy. In the advanced stages of the disorder, epidermal inter-papillary buds disappear and the dermo-epidermal junction reaches almost a horizontal position (Figure 6).

The basic layer of the epidermis is altered by the presence of vacuolized cells, while in certain areas it may even be missing.

In the superficial dermis, there exists a moderate edema and capillary vasodilatation. At the level of the middle dermis there may be noticed an infiltrate formed mostly of lymphocytes, with a peri-adnexial and peri-follicular nodular disposal (Figure 7).

In old lesions, the pilosebaceous follicles are atrophied and even missing.

Studied cytokines did not statistically correlate with the dermo-epidermal alterations in patients with SLE ($p > 0.05$), but the severity of these alterations was significantly correlated with high seric levels of IL-10, IL-6 and TNF-α ($p < 0.05$) (Figure 8, Table 6).
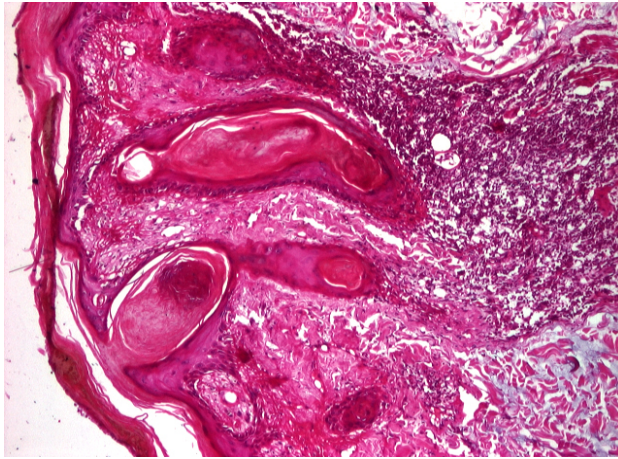
Figure 5 – *Systemic lupus erythematosus: obvious hyperkeratosis with orthokeratosis and corneous invaginations (HE stain, ×40).*
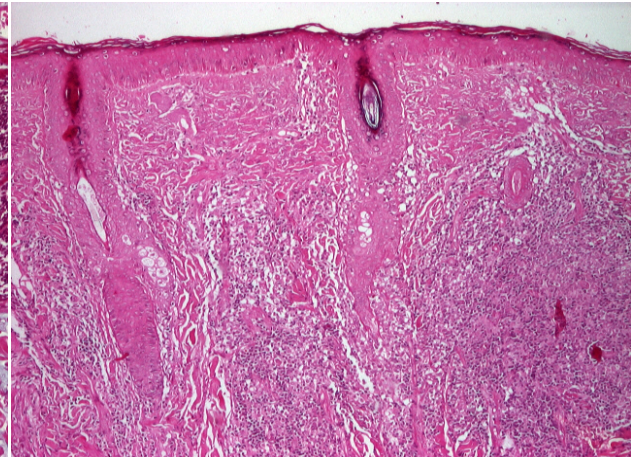

Figure 6 – *Systemic lupus erythematosus: partial atrophy of Malpighian layer and thickening of the corneous layer, lymphocytary infiltrate with nodular disposal (HE stain, ×40).*

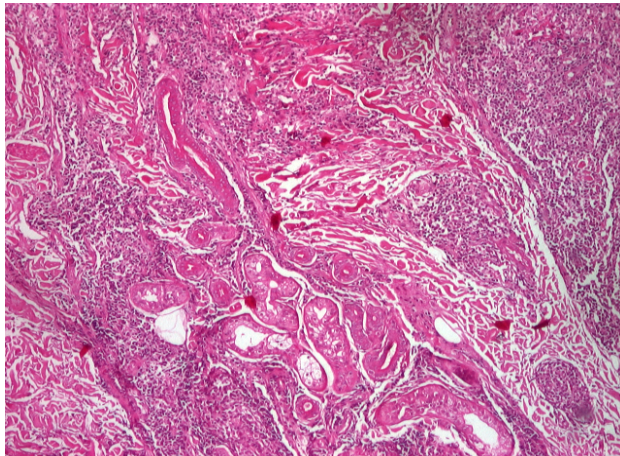Figure 7 – *Systemic lupus erythematosus: dermis lymphocytary infiltrate with peri-adnexial and perifollicular nodular disposal (HE stain, ×40).*
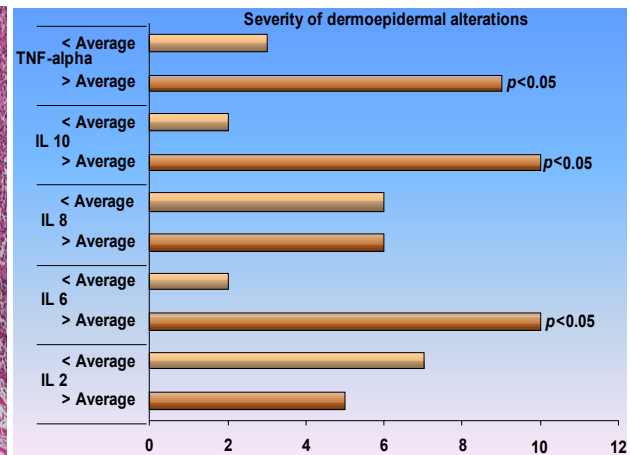

Figure 8 – *Correlation of studied cytokines with the severity of dermo-epidermal alterations in the group of SLE patients.*

Table 6 – *Correlation of studied cytokines with the severity of dermo-epidermal alterations in the group of SLE patients*

	Skin conditions			Severe skin conditions		
	> Average (no. of cases)	< Average (no. of cases)	p	> Average (no. of cases)	< Average (no. of cases)	p
IL-2	9	19	>0.05 (NS)	5	7	0.3983461356 (NS)
IL-6	16	12	>0.05 (NS)	10	2	0.0177115508 (S)
IL-8	10	18	>0.05 (NS)	6	6	0.2985261434 (NS)
IL-10	15	13	>0.05 (NS)	10	2	0.0041112798 (VHS)
TNF-α	15	13	>0.05 (NS)	9	3	0.0157028546 (S)

NS – no significant; S – significant; VHS – very highly significant.

⯐ Discussion

The IL-2 production of T-lymphocytes is a deficient one in SLE (Table 1, Figure 1) in the majority of cases, except for five cases where there were recorded high seric levels.

The B-lymphocytes hyperactivity and the cellularly mediated immune deficiency represent characteristics of SLE. This kind of disbalance is noticeable in the cytokines production, soluble molecules that regulate the growth and function of various immune cells. SLE is an autoimmune disorder with a total disbalance in the network made up of various cytokines, playing a main role in the pathogenesis of the disorder [13].

IL-2 is an immunomodulatory cytokine mainly produced by activated CD4+ T-lymphocytes – Th1 subpopulation. A chemoattractant and chemokinetic factor for T-lymphocytes, IL-2 stimulates: the IFN-γ production; the cytotoxic activation, proliferation and capacity of activated CD8+ T-lymphocytes and of NK-cells; the proliferation of activated B-lymphocytes, increasing the synthesis of antibodies [14].

Proinflammatory cytokines (IL-6, IL-8, TNF-α) presented high seric levels that may be responsible for the characteristic hyperactivity of B-lymphocytes and for

the production of autoantibodies in this autoimmune disorder [15, 16].

In SLE, as well as in other autoimmune disorders, high seric concentrations of IL-6 are decelated, probably because of immune disbalances, which are based, among others, on the inflammatory mechanism. This cytokine, produced by a great variety of cells, both lymphoid (CD4+ T-lymphocytes – Th2 subtype and B-lymphocytes) and non-lymphoid (macrophages, endothelial cells, etc.), is a multifunctional cytokine that acts upon numerous target cells, being involved in the inflammatory response (it stimulates the synthesis of acute phase proteins), in hematopoiesis and in the immune response [11, 17, 18]. IL-6 is a cytokine that plays a significant part in the production of antibodies in SLE, thus triggering a polyclonal hyperactivity of B-lymphocytes, by developing autoimmunity. Moreover, it is responsible for the proliferation and differentiation of activated T-lymphocytes; the IL-2 production and the receptor expression for IL-2 (IL-2R); the differentiation of cytotoxic T-lymphocytes, thus stimulating their cytotoxic function, and the formation of perforines.

IL-6, together with IL-1 and the tumoral necrosis factors, with which it has synergic and complementary actions, represents a key element in the elaboration of inflammatory and anti-infectious responses. IL-6 may also function as a distance messenger, unlike IL-1 and TNF that control local reactions.

Together with IL-6, IL-8, an important mediator of the inflammation, forms the second "attack line" in the inflammatory process, after the IL-1 and TNF "wave". "The neutrophils-activating proteins", as often called, is secreted by the monocytes activated with cytokines (IL-1, TNF-α, and IL-6), by activated antigen T-lymphocytes, as well as by fibroblasts or endothelial cells. It activates neutrophils and induces the lactoferrin-releasing degranulation; it protects endothelial cells by the PMN destructive potential; it increases the vessels permeability [19, 20], etc. Although the averages of IL-8 seric levels are not very high in comparison to the averages of other measured interleukins in the study group and the witness group, there are recent studies that present high seric levels secreted *in vitro* by the lupic dendritic cells [16].

It was proved that in the inflammatory infiltrate of SLE patients, T-lymphocytes release cytokines actively involved in the development of skin lesions. The pattern of the cytokines profile differs from one species to another and the murine skin lupic model, similar to the one in SLE patients, shows a variety of immunological abnormalities, including cytokines [21, 22].

The affection of the skin appears because of the UV radiations that induce the migration of leukocytes and, implicitly, the cytokine release in the cutaneous tissue, resulting in the recruitment of inflammatory cells, the release of other cytokines that may increase and continue this recruitment. The TNF-α production in keratinocytes is different from one individual to another, this variability being closely related to the lupus dermo-epidermal alterations [23–25].

A key mediator of the inflammation, TNF-α has similar effects as IL-1, IL-6: it activates the macropha-ges differentiation and increases their cytocide capacity; it activates the chemotaxis of neutrophils, thus stimulating the activation and expression of adhesion molecules that initiate the transdothelial migration towards the inflammation spot; it activates the cytokine production (IL-1, IL-6, IL-8 and TNF-α itself); it stimulates hepatocytes in the synthesis of acute-phase proteins; it stimulates the arachidonic metabolism and the production of vasodilating, proinflammatory and procoagulant prostaglandins.

Among the immune effects of this cytokine, we mention: stimulation of the production of IL-2, IL-2R and IFN-γ in activated T-lymphocytes; stimulation of the proliferation and differentiation of activated B-lymphocytes.

In conclusion, various members of this super-family mediate the proliferation, survival or apoptosis of cells. Any of the suppressive agents within the production of these cytokines or blockings of their activity have a therapeutic value for a large variety of disorders [26, 27].

The IL-10 production is high in the SLE patients, this increase being among the factors that cause immune perturbations in this disorder [14].

IL-10 is a major anti-inflammatory endogenous mediator through inhibiting the production of proinflammatory cytokines (IL-1, IL-6, TNF-α, IL-8), through a preferential action over monocytes/macrophages. It seems that IL-10 is one of the few strictly "immune" cytokines, mostly produced in the immune system and with a limited action only on the immune cells. Multiple cellular sources are involved in its production: CD4+ T-lymphocytes (repause-CD45RA, memory-CD45RO); CD8+ T-lymphocytes; B-lymphocytes; monocytes; eosinophils; mastocytes, etc.

In humans, IL-10 inhibits the proliferation of Th0, Th1 and Th2-cells, as well as of NK-cells, probably through the diminishing of an accessory factor for the macrophages membrane, involved in the interaction with these cells. It is well-known that part of Th-lymphocytes, the Th1-subtype (secreting IL-2, IFN-γ, TNF) mediate the cellular immunity, by activating NK-cells, cytotoxic T-lymphocytes and delayed-hypersensitivity reactions, while the others, the Th2-subtype (mainly synthesizing IL-1, IL-4, IL-6, IL-8, IL-9, and IL-10), mainly stimulate the production of immunoglobulins [11, 17, 28, 29]. A mutual relationship between the two sets is established, namely: IL-10 (like IL-4) stimulates the differentiation of Th2-cells and inhibits the development of Th1-subset, while IFN-α and IL-12 are stimulators for Th1-lymphocytes and inhibitors of the IL-4 production and of the Th2 differentiation. A change from the Th1 profile to the Th2 profile in the cytokine secretion is also induced by corticosteroids [6, 12].

The characteristics of IL-10 are the inhibitory and anti-inflammatory functions, but, on a limited number of immune cells, this cytokine has stimulating effects as well.

Immuno-suppressive effects: inhibiting the cellular response through minimizing the presentation capacity of the antigen by monocytes/macrophages (a reduction in the expression of second class HLA molecules, of ICAM-1 adhesion molecules); blocking the capacity of

activating CD4+ T-lymphocytes and suppressing the triggering of the specific immune response; inhibiting the IL-2 secretion by CD4+ T-lymphocytes, actions that amplify the suppressing effect of IL-10.

The anti-inflammatory effects are included in the general context of cytokine synthesis inhibiting. In this case, an important part is played by the reduction of TNF, IL-1, IL-6, IL-8 synthesis.

Immunostimulating effects: stimulating CD8+ T-lymphocytes (cytotoxic activity and chemotactism); increasing the cytotoxic capacity and proliferation of NK-cells; stimulating the B-lymphocytes proliferation and differentiation.

Particularly, there was proved that, in SLE, IL-10, together with IL-6, could be key indicators for the balancing of B-lymphocytes activity in the secretion of autoantibodies [18].

There is much evidence that the IL-10 over-production plays a crucial part in this disorder. Various researchers state that in SLE there is an overproduction of IL-10 [14, 17, 18, 28, 30]. This may be the result of two causes. The first one may be due to some intrinsic anomalies in the IL-10 production of some immune cells, while the second cause of high IL-10 production may be the result of some tissular alterations through inflammatory processes. Starting from the properties of IL-10, among which the B-lymphocytes activation and the T-lymphocytes inhibiting, the IL-10 overproduction in SLE may explain the immune anomalies of this disorder characterized by the production of anti-self antibodies and by the deficient response of T-cells [28].

In the cytokine network, the production of one cytokine may stimulate or block the production of other cytokines. For example, IL-10 plays a major role in the inhibiting of cytokine production by CD4+ T-lymphocytes, the Th1-subtype (IL-2, IFN-γ).

At present, the acknowledgement of the main role played by the dendritic cells in the control of tolerance and immunity has led to the hypothesis that SLE may also be determined by the activation of dendritic cells [16, 31]. Recent research place IFN-α in the center of immunological abnormalities found in SLE and proposes IFN-α and/or IFN-α-producing cells as new targets in the treatment of this disorder. The authors suppose that the IFN type I antagonists will bring an improvement in the SLE patients, like TNF antagonists brought in the patients with rheumatoid arthritis [31].

Cytokines present an applied interest and it is highly probable that, in the future they will play a significant part in the immunotherapy of autoimmune disorders, cancer or immunodeficiencies. Although the first attempts of interferon, IL-1 or IL-2 therapy were accompanied by significant adverse effects, at present there are performed less toxic dosages and associations, but with maximal action, through the combined therapy with cytostatics, monoclonal antibodies/immunotoxines. In order to obtain benefic effects, the simultaneous "manipulation" of various cytokines may also be necessary in certain situations.

The combination or blocking of various soluble factors activity could be useful not only in neoplasias but also in the autoimmune pathology, where various cytokines usually contribute to the initiation and progress of the disorder.

⊟ Conclusions

SLE is an autoimmune disorder also characterized by a disbalance in the cytokine network.

Signaling and balancing abnormalities of B-lymphocytes by cytokines are responsible by the excessive production of autoantibodies.

The T-lymphocytes production in IL-2 is deficient in SLE in the majority of cases.

Proinflammatory cytokines (IL-6, IL-8, TNF-α) presented high seric levels, thus assuring the proliferation and differentiation of B-lymphocytes, responsible for their characteristic hyperactivity with the production of antibodies in this autoimmune disorder.

IL-10 was proved to be a key factor in the intensification of inflammation and in the balancing of B-lymphocytes activity; the IL-10 overproduction in SLE may explain the immune anomalies of this disorder, characterized by the production of anti-self antibodies and by the deficient response of T-cells.

The laboratory investigations undertaken for the SLE diagnosis include both urine tests, as well as special tests for the appreciation of the immune status (cytokines), while IL-10 could serve as a specific biological witness in the screening regarding the improvement of the disorder.

IL-10, IL-6 and TNF-α play an important part in the development of severe dermo-epidermal alterations (disappearance of epidermal inter-papillary buds, horizontalization of dermo-epidermal junction, atrophy or even disappearance of pilosebaceous follicles).

Cytokines present an applied interest and it is highly probable that, in the future, they will play a significant part in the immunotherapy of autoimmune disorders, cancer or immunodeficiencies.

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