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Analysis of immunopathogenesis of psoriasis in the dynamics of treatment

Objective — to analyze the parameters of the immune system of the organism in patients with psoriasis before and after treatment.

Materials and methods. The parameters of cellular immunity in an organism estimated after the change of relative and absolute amount of T- ($CD3^+$) and B- ($CD19^+$) of lymphocytes and subpopulations ($CD4^+$, $CD8^+$, $CD16^+$, $CD25^+$, $CD71^+$, $CD30^+$, $CD95^+$).

To identify of surface structures of lymphocytes the method of direct immune fluorescence was used where fluorescent label was attached to anti-CD of mononuclear antibodies of series Leu of the firm «Becton Dikinson» (USA). Calculations were conducted on the laser instantaneous cytofluorometer of the firm «Baston» (USA).

Results and discussions. The most positive influence on the parameters of the cellular link of the immune system of the organism was found in patients with psoriasis who received immunobiological therapy with the medication etanercept in combination with narrowband (311 nm) phototherapy. After treatment in patients of this group, due to a significant decrease in the production of TNF and its serum concentration, the pro-inflammatory changes in the cellular link of the immune system decreased, the number of lymphocytes with the an early activation marker, which initiated a further cytokine cascade of development and prolongation of inflammation decreased significantly. In addition, the established reduction in the number of $CD30^+$ lymphocytes is an indirect factor indicating the switching of the Tx2 response (autoimmune manifestations) to Tx1, and hence the achievement of the clinical and immunological remission of the psoriatic process. It is extremely important for the functioning of the immune system the decrease in the content of activated lymphocytes that express the Fas-receptor as due to the increased lymphocyte apoptosis, namely, T-cytotoxic lymphocytes, and autoimmune and proliferative changes took place inherent in the exacerbation of the psoriatic process.

Conclusions. It was established that all our schemes of psoriasis treatment have immunorehabiting properties but their degree of severity was different. The most effective treatment scheme is the combined use of etanercept and UVB therapy, thus proliferative and inflammatory changes in the skin reduced, antigenic loading decreased, the level of CICs, autosensibilization and autoimmune disorders also decreased.

Keywords

Psoriasis, systemic immunosuppressive therapy, immunological changes.

The etiology and pathogenesis of psoriasis are not yet fully understood. At present there are two main hypotheses regarding the nature of the process that leads to the development of this disease. According to the first hypothesis, psoriasis is a primary skin disease, in which the normal process of maturation and differentiation of skin cells with excessive proliferation of these cells is violated.

Autoimmune aggression of T-lymphocytes and macrophages against skin cells, their invasion into the thickness of the skin and their proliferation in the skin are seen as secondary body's reaction to excessive reproduction of pathologically altered keratinocytes [4]. The second hypothesis suggests that psoriasis is an immune-mediated, immunopathological disease with an autoimmune component, in which the proliferation of the epidermis cells is secondary to the immune damage of the cells of the skin. At present, the generally accepted position is that the onset of inflammation in the skin in patients with psoriasis begins with the activation of inflammatory cells in the skin [5].

The main characteristics of the pathological process in psoriasis are recognized: immune inflammation, accompanied by activation of T-lymphocytes, excessive production of mediators of the immune response. The pathological process is also characterized by the presence of an autoimmune component and the presence of inadequate activation of the immune cellular link that causes the total process with the Th-1 cytokine profile; available gamma interferon in the cytoplasm stimulates the migration of macrophages from the focus of inflammation [2—6].

The clinical course of psoriasis is characterized by considerable variability and severity. Despite the wide variety of currently available methods for treating psoriasis, there is a discrepancy between efficiency and their level. Pathogenetic methods for treating psoriasis include systemic and local treatment and additional therapies (light therapy, physiotherapy, balneotherapy, psychotherapy, climate therapy, etc.) [1].

The amount of therapeutic measures at psoriasis is determined by the basic parameters of the skin (stage, type, duration, and course) and articular pathological processes, as well as the severity of systemic manifestations.

With light degree of skin psoriatic process, in particular, in patients with limited nodule form of psoriasis, as a rule, only external therapy and skin care products are used, taking into account the stage of the process. External therapy is divided into non-suppressive (local remedies with keratolytic, resorbing, softening and/or moisturizing effects) and suppressive (topical glucocorticosteroids, topical retinoids) [7].

With mild and severe psoriasis, systemic therapy is used which is divided into non-suppressive (in order to eliminate the dominant manifestations of accompanying lesions, in particular intoxication with biochemical and metabolic disorders) and suppressive therapy directed at reducing the activity of skin psoriatic process and destruction of the articular apparatus.

Systemic suppressive psoriasis therapy involves the use of glucocorticosteroids, disease-modifying drugs (cytostatic immunosuppressants, aromatic retinoids), sorption methods (plasma and hemosorption, plasmapheresis), as well as drugs with biological agents (monoclonal antibodies) [7].

It should be noted that prescription of systemic corticosteroid hormones and disease-modifying drugs in the treatment of mild and severe psoriasis requires a comprehensive individualized justification. Systemic therapy with the use of these drugs can lead to destabilization of psoriasis with the formation of torpid, severe and atypical forms of dermatitis. This is due to the fact that systemic corticosteroids and disease-modifying drugs do not have selective action. In particular, the inhibition of these drugs of the immune response is not limited to inhibition of activated T-lymphocytes and runs in parallel with the violation of carbohydrate, protein and lipid metabolism.

At present a new promising direction in the treatment of psoriasis is the use of biological agents — monoclonal antibodies. Relevant monoclonal antibodies have selective action, which avoids numerous complications and side effects [6, 7]. However, studying the mechanisms of regulation and the influence of monoclonal antibodies on the pathogenetic processes in the body of patients with psoriasis at the systemic and local levels, as well as the determination of their therapeutic efficacy in the treatment of this dermatitis, require an in-depth study.

Objective — to analyze the parameters of the immune system of the organism in patients with psoriasis before and after treatment.

Materials and methods

Patients with vulgar psoriasis were under our comprehensive survey. There were 207 patients: men — 126 (61 %), women — 81 (39 %). The age of the examined patients ranged from 18 to 79 years. Parameters of cellular immunity in the body were evaluated by changing the relative and absolute amount of T- ($CD3^+$) and B- ($CD19^+$) lymphocytes, as well as subpopulations ($CD4^+$, $CD8^+$, $CD16^+$, $CD25^+$, $CD71^+$, $CD30^+$, $CD95^+$). For the identification of surface structures of lymphocytes, a direct immunofluorescence method was used in which the fluorescence label was attached to anti-CD monoclonal antibodies of the Leu series of the firm «Becton Dikinson» (USA). The calculations were conducted on the laser instantaneous cytofluorometer of the firm «Baston» (USA).

Results and discussions

In order to assess the therapeutic efficacy of the medication of immunobiological effects of etanercept and its combination with narrowband UVB therapy compared to the standard therapies for the treatment of this dermatitis, all 207 patients we examined were divided into four equal clinical groups, taking into account the age and gender of the patients, as well as according to the severity, nature and duration of the course of psoriasis.

The treatment of psoriatic patients enrolled in the first observation group (54 patients) was performed according to the standard scheme by the individualized administration of topical glucocorticosteroids of different effect (betamethasone, hydrocortisone butyrate, dexamethasone, clobetasol, methylprednisolone, prednicarbate, triamcinolone,

Table 1. **The content of the main and activated populations and subpopulations of lymphocytes in patients with psoriasis in the dynamics of treatment (M ± m)**

Investigated parameters	Parameters in patients with psoriasis before treatment (n = 207)	Parameters in patients with psoriasis after treatment				Control group (n = 35)
		The first clinical group (n = 54)	The second clinical group (n = 51)	The third clinical group (n = 50)	The fourth clinical group (main) (n = 52)	
Leukocytes, · 10^9/L	6.41 ± 0.38	8.12 ± 0.49*	8.28 ± 0.53*	5.32 ± 0.27*	5.91 ± 0.51	6.58 ± 0.47
Lymphocytes, %	38.6 ± 1.74	22.6 ± 1.80*	24.1 ± 2.03*	28.6 ± 2.03	29.6 ± 2.16	30.37 ± 1.52
$CD3^+$ lymphocytes, %	64.3 ± 2.18	65.1 ± 2.16	64.1 ± 1.76	61.8 ± 1.84	62.1 ± 2.06	63.48 ± 3.39
$CD4^+$ lymphocytes, %	42.2 ± 1.15*	41.6 ± 1.21*	38.8 ± 1.31*	32.4 ± 1.22#	32.7 ± 1.14#	33.12 ± 1.67
$CD8^+$ lymphocytes, %	14.9 ± 1.06	15.2 ± 1.03*	14.8 ± 1.01*	18.1 ± 1.08#	19.5 ± 1.08#	19.08 ± 1.02
CD4/CD8	2.82 ± 0.04	2.71 ± 0.08*	2.62 ± 0.06*	1.79 ± 0.05#	1.67 ± 0.05#	1.71 ± 0.07
$CD19^+$ lymphocytes, %	15.8 ± 0.21	15.2 ± 0.36*	15.1 ± 0.28*	10.7 ± 0.30#	9.3 ± 0.22#	9.61 ± 0.31
$CD16^+$ lymphocytes, %	17.1 ± 0.98	16.9 ± 1.03	16.8 ± 0.73	12.6 ± 0.82*#	12.2 ± 0.83*#	17.26 ± 1.13
$CD25^+CD71^+$ lymphocytes, %	21.50 ± 0.65	18.9 ± 0.53*#	18.2 ± 0.56*#	13.4 ± 0.41#	12.3 ± 0.42#	12.71 ± 0.39
$CD95^+$ lymphocytes, %	7.83 ± 0.42	9.93 ± 0.27*#	9.95 ± 0.11*#	3.81 ± 0.23#	3.48 ± 0.17#	4.38 ± 0.18
$CD30^+$ lymphocytes, %	7.13 ± 0.11	6.99 ± 0.22*	6.95 ± 0.41*	1.95 ± 0.09#	1.69 ± 0.05#	1.2 ± 0.04

Note. * Probability of difference of the parameter with the control group ($p < 0.05$); # probability of difference of the parameter in the dynamics of treatment ($p < 0.05$); n — number of patients.

fluticasol), taking into account the duration and severity of the course of dermatitis. Patients in this group were prescribed inhibitors of calcineurin, vitamin D3 or one of its analogues, as well as additional therapy aimed at therapeutic correction diagnosed with concomitant diverse pathology. Terms of treatment of patients enrolled in the first group varied from 20 to 40 days taking into account the severity of the course of dermatitis.

Treatment of patients with psoriasis enrolled in the second group (51 patients) was also performed according to a standard scheme of therapy with topical glucocorticosteroids, antihistamines and additional drugs, taking into account concomitant pathology. In addition, all patients in the second group after the individualized determination of biodose took erythemous doses of UV irradiation by quartz lamps zonal according to the scheme developed by I.I. Pototsky daily or in a day on a course of 12—15 sessions. Duration of treatment of patients of the second group varied from 30 to 40 days.

Treatment of patients with psoriasis in the third group (50 patients) was performed by the drug of immunobiological action of etanercept in a dose of 50 mg subcutaneously once a week for 3 months.

Treatment of patients with psoriasis enrolled in the fourth (main) group (52 patients) was performed by a similar therapy with the drug of immunobiological action of etanercept within three months, as well as narrowband UVB therapy in a day, for a course of 10 sessions.

We conducted a comparative assessment of the parameters of the cellular and humoral links of the immune system of the body in the examined patients with psoriasis in the dynamics of various treatment schemes. The corresponding dynamics of changes in the parameters of cellular immunity in the examined patients with psoriasis is presented in Table 1.

Before the beginning of the course of treatment in the first, second, third and fourth (main) clinical groups, there was no significant difference between the parameters presented in Table 1. Analysis of the data presented in Table 1 indicates that the following changes in the pearameters of immunological reactivity of the organism were detected in the primary immunological examination in patients with psoriasis: the total number of leukocytes did not have a significant difference from the data in healthy persons ($p > 0.1$), but the relative content of lymphocytes was higher than the indicator of the control group by 27.19 % ($p < 0.05$). Investigation of $CD3^+$ lymphocytes showed that their level did not differ from that of the control group ($p > 0.1$). At the same time, there was a significant increase in the content of $CD4^+$ lymphocytes — helpers by 27.48 % ($p < 0.05$) and a decrease in the percentage of T-cytotoxic lymphocytes/suppressors by 22 % ($p < 0.05$) compared with data of the control group

that displays autoimmune and pro-inflammatory changes in the immune system. These changes in the quantitative composition of immunoregulatory subpopulations led to an increase in the indicator of immunoregulatory index by 64.9 % ($p < 0.05$) compared with the parameter in healthy persons. It was also found an increase in the relative number of $CD19^+$ cells in the peripheral blood of patients by 64.4 % ($p < 0.06$) compared to a similar parameter of the control group. The percentage of $CD16^+$ lymphocytes had no significant difference from the parameters in healthy persons ($p > 0.1$).

We have established a reliable increase in the percentage of activated subpopulations of lymphocytes in the peripheral blood of patients with psoriasis. Thus, the content of $CD25^+CD71^+$ lymphocytes, which are markers of early activation of lymphocytes, exceeded the control group by 69.2 % ($p < 0.05$), and $CD95^+$ cells expressing the FAS receptor and ready to enter into apoptosis exceeded normative parameters of 78.82 % ($p < 0,05$).

We have also established a significant increase in the relative number of $CD30^+$ lymphocytes which are activated cells that carry the signal to apoptosis and also show the level of Tx2 cells of the immune system in 5.94 times ($p < 0.05$) compared with the corresponding parameter in patients of the control group. These changes confirm the available separate literature data that the course of psoriasis is closely related to the hyperactivity of the Tx2 link of the immune system with increased activation of immune-competent cells and the excess synthesis of Tx2 derivatives of cytokines. In the dynamics of our treatment of patients with psoriasis using different therapies, their multi-directional effect on the parameters of the cellular level of immunity of the patient's body was established. Patients in the first clinical group treated according to the standard scheme showed a significant increase in the total amount of leukocytes that exceeded their parameters in healthy persons by 23.4 % ($p < 0.05$). The percentage of lymphocytes at this time decreased by 41.45 % ($p < 0.05$). These changes are related to the known effect of glucocorticosteroids on the hematopoietic system with elevated levels of erythrocytes, leukocytes and platelets but a decrease in the content of monocytes and lymphocytes.

In the examined patients with psoriasis the saved level of $CD3^+$ cells in the peripheral blood ($p > 0.1$) was observed before therapy, in compare with the control group data. In the dynamics of treatment in the first clinical group, the T-cell content remained unchanged ($p > 0.1$). The percentage of $CD4^+$ lymphocytes did not significantly change ($p > 0.1$) and remained higher than in healthy persons by 25.5 % ($p < 0.05$) in patients of the first clinical group.

The relative content of $CD8^+$ lymphocytes during the examination of patients, prior to the course of therapy was lower than the parameters in the control group ($p < 0.05$) and in the treatment dynamics did not change remaining below the standard parameter by 20.34 % ($p < 0.05$). At the same time, the parameter of the immunoregulatory index also exceeded the normative parameter by 58.5 % ($p < 0.05$) and did not differ from the baseline.

The absence of significant changes in the quantitative composition of T-lymphocytes and main immunoregulatory subpopulations is due to activation of the immune system, which was not adjusted for the purpose of the standard treatment scheme.

In patients with psoriasis receiving standard therapy, the content of B-lymphocytes was not changed in the dynamics of treatment and exceeded the corresponding parameter in patients of the control group by 58.2 % ($p < 0.05$), which may be due to insufficient clinical and the anti-inflammatory effect, as well as the fact that glucocorticosteroids, due to their peculiarities of their actions, have insufficient suppressive effects on the B-link of the immune system. The relative amount of $CD16^+$ cells in the treatment dynamics was not changed and remained within the parameters of healthy persons.

A reliable decrease in the content of activated lymphocytes with an early activation marker in the dynamics of the corresponding treatment was found to be 12.1 % ($p < 0.05$), but their number remained above the normative parameter by 48.7 % ($p < 0.05$).

However, against the backdrop of standard therapy, with the involvement of glucocorticosteroids, an increase in the relative number of $CD95^+$ lymphocytes was observed by 26.8 % ($p < 0.05$) which is due to the properties of the drugs to enhance expression of the Fas-receptor. The percentage of $CD30^+$ lymphocytes in the dynamics of the standard treatment scheme remained unchanged and exceeded the level of a similar parameter of healthy persons in 5.83 times ($p < 0.05$).

Thus, with the application of the standard treatment scheme in patients with psoriasis of the first group, in addition to insufficient clinical efficacy, its insignificant effect on the change in the parameters of the main populations and subpopulations of lymphocytes characterized by a decrease in the content of activated lymphocytes with the phenotype $CD25^+CD71^+$ and increased $CD95^+$ cells was established.

Similar minimal changes in the parameters of the cellular link of the immune system were established in patients with psoriasis of the second clinical group after a standard treatment scheme with simultaneous use of zonal UV irradiation with quartz lamps. Patients in this group showed a reliable increase in

the total number of leukocytes, which exceeded the parameters of healthy persons by 25.8 % ($p < 0.05$), and the percentage of lymphocytes was significantly reduced by 37.5 % ($p < 0.05$).

The level of $CD3^+$ cells, $CD4^+$ lymphocytes and $CD8^+$ lymphocytes in peripheral blood in patients with psoriasis of the second group after treatment was not significantly changed ($p > 0.1$) and the parameter of immunoregulatory index exceeded the normative parameters by 53.2 % ($p < 0.05$) and did not differ from the corresponding parameter at the initial level.

In the dynamics of treatment of patients enrolled in the second clinical group, the content of B-lymphocytes was not also changed and exceeded the corresponding parameters in the persons of the control group by 57.12 % ($p < 0.05$) and the relative number of $CD16^+$ cells remained in the dynamics of treatment within the limits set in healthy persons.

However, after treatment in patients of the second group, similarly to patients of the first clinical group a reliable decrease in the content of activated lymphocytes with an early marker of activation of $CD25^+CD71^+$ was found to be 15.4 % ($p < 0.05$) but their number remained higher than the normative parameter by 43.2 % ($p < 0.05$).

An increase in the relative number of $CD95^+$ lymphocytes was found to be 27.1 % ($p < 0.05$) which is due to the use of topical glucocorticosteroids in the treatment of these patients. The relative number of $CD30^+$ lymphocytes in the dynamics of treatment of patients in the second group also remained unchanged and exceeded the level of a similar parameter in healthy persons in 5.8 times ($p < 0.05$).

Thus, in patients of the second clinical group, minor immunosuppressive and pro-apoptotic effects of the applied treatment scheme on the subpopulation of lymphocytes were detected after the treatment.

In patients with psoriasis enrolled in the third group treated with the medication etanercept as well as in patients enrolled in the fourth (main) group who received etanercept simultaneously with the course of narrowband (311 nm) phototherapy after the completion of therapy course there were significant positive changes in the cellular link of the immune system.

In particular, in patients enrolled in the third clinical group, the total number of leukocytes in the dynamics of treatment was reduced and was lower than the level of their parameters in healthy persons by 19.2 % ($p < 0.05$), and in patients enrolled in the fourth (the main) group did not have any reliable differences from their parameters in healthy persons ($p > 0.1$). The relative number of lymphocytes in the dynamics of treatment was also reached in patients of the third and fourth groups of normative parameters. At the same time the amount of lymphocytes significantly decreased by 26.0 % ($p < 0.05$) in patients of the third group and of the fourth — by 23.3 % ($p < 0.05$) compared to the baseline.

It should be noted that the percentage of $CD3^+$ cells in the dynamics of treatment in both groups had no reliable changes and corresponded to the level in healthy persons. The reliable reduction in the relative number of $CD4^+$ lymphocytes was found to be 23.2 % ($p < 0.05$) in the third group and 22.5 % ($p < 0.05$) in the fourth group, with a compensatory increase in the $CD8^+$ lymphocytes by 21.5 % ($p < 0.05$) in the third group of patients and by 30.9 % ($p < 0.05$) in the fourth to the level of healthy persons. As a result of the revealed changes in the main immunoregulatory subpopulations the recovery of the parameter of immunoregulatory index to the parameter of the control group took place.

There is also a significant decrease in the relative number of B-cells and it is an indirect marker which confirms the high anti-inflammatory effect of these types of treatment, although the level of reduction of B-lymphocytosis depended on its type. Thus, in the third group of patients the number of $CD19^+$ lymphocytes decreased by 32.3 % ($p < 0.05$), and in the fourth group — by 41.1 % ($p < 0.05$) to the parameters of the control group. According to the data presented in Table 1 in patients enrolled in the 3rd and 4th (main) clinical groups a significant decrease in the relative number of $CD25^+CD71^+$ lymphocytes was found by 37.7 % ($p < 0.05$) and 42.8 % ($p < 0.05$) in compare with the level of the healthy persons. In the dynamics of treatment of patients in the third and fourth groups there were significant changes in the percentage of activated $CD95^+$ lymphocytes. The use of etanercept which is an inhibitor of TNF in the treatment of patients of these groups resulted in a significant decrease in the expression of Fas-receptor on lymphocytes that is to reduce their readiness to enter apoptosis. In patients of the third group their level decreased by 51.35 % ($p < 0.05$) and the fourth group — by 55.6 % ($p < 0.05$) while this parameter in both groups reached the normative parameters. Reduced $CD95^+$ lymphocyte content may be due primarily to a decrease in serum concentrations of FNP-α as the main inducer of apoptosis in lymphocytes. In patients of the third group a reliable decrease of the percentage of $CD30^+$ lymphocytes was in 3.66 ($p < 0.05$) times in compare with the initial data and in patients of the fourth group in 4.22 times ($p < 0.05$).

Thus, the most positive influence on the parameters of the cellular link of the immune system of the organism was found in patients with psoriasis enrolled in the fourth (main) group who received immunobiological therapy with the medication

Table 2. **Dynamics of changes in the parameters of functional activity of immunocompetent cells in patients with psoriasis (M ± m)**

Parameters	Parameters in patients with psoriasis before treatment (n = 207)	Parameters in patients with psoriasis after treatment				Control group (n = 35)
		The first clinical group (n = 54)	The second clinical group (n = 51)	The third clinical group (n = 50)	The fourth clinical group (main)(n = 52)	
RBTL with FGA, %	81.8 ± 2.27	79.2 ± 2.45*	78.1 ± 1.23*	74.7 ± 1.29#	75.2 ± 1.63#	74.96 ± 1.54
Spontaneous RBTL, %	4.85 ± 0.11	3.91 ± 0.12*#	3.85 ± 0.11*#	2.81 ± 0.12#	2.84 ± 0.14#	2.79 ± 0.11
Phagocytic index, %	51.6 ± 1.38	47.1 ± 1.15*#	47.3 ± 1.04*#	55.9 ± 1.82*#	56.1 ± 1.73*#	62.60 ± 1.7
Phagocytic number	4.13 ± 0.1	3.89 ± 0.09*#	3.93 ± 0.07*	4.86 ± 0.11*#	4.90 ± 0.08*#	6.31 ± 0,22

Note. * Probability of difference of the parameter with the control group ($p < 0.05$); # probability of difference of the parameter in the dynamics of treatment ($p < 0.05$); n — number of patients.

etanercept in combination with narrowband (311 nm) phototherapy. After treatment in patients of this group, due to a significant decrease in the production of TNF and its serum concentration the inflammatory changes in the cellular link of the immune system decreased; the number of lymphocytes with an early activation marker which initiated a further cytokine cascade of development and prolongation of inflammation decreased significantly. Moreover, the reliable decrease in the number of $CD30^+$ lymphocytes in patients from the fourth group is an indirect factor indicating the switch of the Tx2 response (autoimmune manifestations) to Tx1that means the achievement of the clinical and immunological remission of the psoriatic process. It is extremely important for the functioning of the immune system to consider the decrease in the content of activated lymphocytes that express the Fas-receptor as due to increased lymphocyte apoptosis, namely, T-cytotoxic lymphocytes, and autoimmune and proliferative changes took place that are characteristic of exacerbation of the psoriatic process.

Functional activity of immunocompetent cells in patients with psoriasis in the dynamics of treatment is shown in Table 2.

Before the beginning of the treatment courses in the first, second, third and fourth (main) clinical groups no significant difference was observed between the parameters presented in Table 2. According to the data presented in Table 2, in patients with psoriasis, prior to the course of therapy, spontaneous proliferative activity of lymphocytes by 73.84 % ($p < 0.05$) and stimulated FGA of lymphocyte proliferative activity by 9.12 % ($p < 0.05$) were increased due to the phenomena of autosensibilization and high content of activated lymphocytes as a result of activity of the psoriatic process. In the dynamics of treatment in patients of the first and second clinical groups there was a reliable decrease in the spontaneous production by 19.38 % ($p < 0.05$) and 20.62 % ($p < 0.05$), but both parameters were higher than in healthy persons by 40.14 % ($p < 0.05$) and 37.99 % ($p < 0.05$). In patients of the third and fourth clinical groups receiving the immunobiological medication etanercept this indicator became significantly lower by 42.06 % ($p < 0.05$) and 41.44 % ($p < 0.05$) and reached the parameters of the control group. The parameter of stimulated FGA proliferative activity of lymphocytes after treatment in patients both of the first and second groups did not have a significant difference from the initial parameter and was reliable higher than the normative parameter. At the same time, in the third and fourth group of patients, the reliable reduction of this parameter by 8.7 % ($p < 0.05$) and 8.8 % ($p < 0.05$) was observed in compare with the parameter of the control group. Normalization of parameters of proliferative activity of lymphocytes is connected first of all with the decrease of the phenomena of autoactivation and autosensibilization, restoration of sensitivity of the receptor apparatus of lymphocytes at decrease of antigenic and cytokine stimulation. The phagocytic activity of neutrophils in examined psoriatic patients was reduced to the course of therapy: phagocytic index of Hamburg was lower than that of controls by 17.52 % ($p < 0.05$), and Wright's phagocytic number was lower by 34.58 % ($p < 0.05$).

In the dynamics of treatment in the first and second clinical groups further reduction of these indicators was found. In patients of the first group there was a further reduction of the phagocytic index by 8.72 % ($p < 0.05$) and the phagocytic number — by 5.82 % ($p < 0.05$), and in the second group — by 8.33 % ($p < 0.05$) and 4.84 % ($p > 0.1$) respectively.

In the third group of patients the etanercept partly recovered phagocytic activity; the phagocytic index of Hamburg increased by 8.3 % ($p < 0.05$),

Table 3. **The level of CIC in patients with psoriasis in the dynamics of treatment (M ± m)**

Parameters	Parameters in patients with psoriasis before treatment (n = 207)	Parameters in patients with psoriasis after treatment				Control group (n = 35)
		The first clinical group (n = 54)	The second clinical group (n = 51)	The third clinical group (n = 50)	The fourth clinical group (main) (n = 52)	
CICs large-molecular, cond. unit	28.69 ± 1.51	33.5 ± 1.07*#	34.6 ± 1.12*#	41.7 ± 1.22*#	42.3 ± 1.27*#	53.45 ± 3.12
CICs medium-molecular, cond. unit	56.75 ± 1.83	45.9 ± 1.73*#	46.6 ± 1.55*#	40.3 ± 1.24*#	39.1 ± 1.17*#	35.61 ± 1.22
CICs small molecular, cond. unit	41.14 ± 1.78	32.7 ± 1.04*#	30.1 ± 1.1*#	21.8 ± 0.96*#	19.5 ± 0.81*#	12.04 ± 1.03

Note. * Probability of difference of the parameter with the control group ($p < 0.05$); # probability of difference of the parameter in the dynamics of treatment ($p < 0.05$); n — number of patients.

and Wright's phagocyte numcer was 17.68 % ($p < 0.05$), although both parameters remained significantly lower than those of healthy persons.

In the fourth group of patients the etanercept with UV-B therapy led to an increase in the phagocytic index of Hamburg by 8.7 % ($p < 0.05$) compared with the initial data, and Wright's phagocytic number — by 18.64 % ($p < 0.05$).

Thus, using different treatment schemes for examined patients with psoriasis showed the effectiveness in restoring the functional activity of lymphocytes and reducing the autoimmune manifestations due to first of all powerful anti-inflammatory effects of both glucocorticosteroids and immunobiological therapy and a decrease in the level of inflammatory cytokines and other mediators of inflammation.

The established reduction of phagocytic activity in the dynamics of the use of glucocorticosteroids in the patients of the first and second groups of observation is due to their pharmacological characteristics and proven suppressive effects on the phagocytic link of the immune system, while the partial recovery of the corresponding parameters in patients with etanercept is mediated by the decrease in inflammatory changes in the immune system.

The absence of significant changes in phagocytic activity of neutrophils indicates that it is expedient in the future, at the stages of rehabilitation, to prescribe immunological correctors after stabilization of the patients' condition.

The study of the dynamics of serum concentration of CICs using different therapies is presented in Table 3.

Before the beginning of the treatment course in the first, second, third, and fourth (main) clinical monitoring groups, no significant difference was observed between the parameters presented in Table 3. According to the data presented in Table 3, all patients with psoriasis before the treatment had manifestations of immunotoxicosis, which consisted in a significant increase in the level of pathogenic CICs against the backdrop of a decrease in the concentration of physiological CICs of large size.

In general, in patients with psoriasis prior to therapy, the content of pathogenic medium molecular CICs exceeded its parameter in the control group by 59.35 % ($p < 0.05$), and the small molecular CICs was in 3.41 times ($p < 0.05$) with simultaneous reduction of the concentration of physiological CICs of large size by 46.32 % ($p < 0.05$) compared with the normative parameters.

As we can see from the data presented in Table 3, using a standard treatment scheme contributed to a reliable but insufficient reduction of immunotoxicosis. Thus, the level of pathogenic medium molecular CICs and small molecular CICs decreased significantly by 19.12 % ($p < 0.05$) and 20.52 % ($p < 0.05$), however, it was by 28.9 % higher than that of the control group ($p < 0.05$) and in 2.72 times ($p < 0.05$). At the same time, an increase in the content of large molecular CICs was observed by 16.77 % ($p < 0.05$), but this figure remained below the parameters of healthy persons by 37.42 % ($p < 0.05$).

A similar dynamics of CICs parameters was observed in the second group of patients. The level of pathogenic medium molecular CICs and small molecular CICs decreased significantly, by 17.89 % ($p < 0.05$) and 26.83 % ($p < 0.05$) respectively, but it was by 30.86 % higher ($p < 0.05$) and in 2.5 times ($p < 0.05$) respectively. There was also an increase in the content of large molecular CICs by 20.6 % ($p < 0.05$), but this parameter remained below the parameters of healthy persons by 37.32 % ($p < 0.05$).

A more significant positive dynamics of the parameters of the CICs was observed with the use of immunobiological therapy. At the same time, the level of pathogenic medium molecular CICs and small molecular CICs significantly decreased by 29.0 % ($p < 0.05$) and 47.01 % ($p < 0.05$) respectively, but exceeded the parameters of the control group by 13.17 % ($p < 0,05$) and 1.8 times ($p < 0,05$). There was also an increase in the content of the large

Table 4. **Serum concentration of the main classes of immunoglobulin in patients with psoriasis in the dynamics of treatment (M ± m)**

Parameters	Parameters in patients with psoriasis before treatment (n = 207)	Parameters in patients with psoriasis after treatment				Control group (n = 35)
		The first clinical group (n = 54)	The second clinical group (n = 51)	The third clinical group (n = 50)	The fourth clinical group (main) (n = 52)	
IgG, g/L	15.98 ± 0.37	11.07 ± 0.24	11.13 ± 0.17	11.09 ± 0.31	11.15 ± 0.21	11.76 ± 0.44
IgA, g/L	1.92 ± 0.016	1.95 ± 0.02	1.98 ± 0.03	1.97 ± 0.02	1.99 ± 0.011	2.06 ± 0.13
IgM, g/L	1.68 ± 0.04	1.28 ± 0.06	1.30 ± 0.03	1.29 ± 0.02	1.30 ± 0.04	1.38 ± 0.05

molecular CICs by 45.30 % ($p < 0.05$), but this parameter still remained below the parameter of healthy persons by 21.98 % ($p < 0.05$). Similar positive changes in the concentration of CICs are due to the anti-inflammatory effect with a decrease in autoantigenemia and the formation of specific antibodies, as well as with partial restoration of phagocytic activity of neutrophils.

Positive dynamics of the parameters of CICs was also observed in patients of the fourth group. In this case, the level of pathogenic medium molecular CICs and small molecular CICs was significantly decreased by 31.10 % ($p < 0.05$) and 2.11 times ($p < 0.05$), however, it exceeded the parameters of the control group by 9.8 % ($p < 0.05$) and 61.9 % ($p < 0.05$). There was also an increase in the content of the large molecular CICs by 47.4 % ($p < 0.05$) but this parameter still remained below the parameter of healthy persons by 20.85 % ($p < 0.05$).

Before the beginning of the treatment courses in the first, second, third and fourth (main) clinical groups, no significant difference was observed between the parameters presented in Table 4. The dynamics of serum concentration of the main classes of immunoglobulin in patients with psoriasis at different schemes of treatment is presented in Table 4.

As we can see from the data presented in Table 4, in the serum of patients with psoriasis prior to the course of therapy, a reliable increase in IgG content was observed at 35.88 % ($p < 0.05$) and IgM was 21.74 % ($p < 0.05$). In the dynamics of treatment when using different schemes of combined therapy, the IgG, IgM and IgA content of serum in the examined patients decreased and met the regulatory parameters. This fact is undoubtedly evidence of the positive effect of the proposed treatment schemes that have anti-inflammatory effects and do not induce stimulation of individual links of the immune system.

Conclusions

The proposed therapeutic scheme is the most effective by means of combining etanercept and UVB therapy, thereby proliferative and inflammatory changes in the skin, antigen load, the level of CICs, autosensibilization and autoimmune disorders decreased significantly.

There is no conflict of interest.

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Аналіз імунопатогенезу псоріазу в динаміці лікування

Мета роботи — проаналізувати параметри імунної системи у пацієнтів із псоріазом до та після лікування.

Матеріали та методи. Параметри клітинного імунітету оцінювали шляхом вимірювання відносної та абсолютної кількості Т- ($CD3^+$) і В- ($CD19^+$) лімфоцитів та їхніх субпопуляцій ($CD4^+$, $CD8^+$, $CD16^+$, $CD25^+$, $CD71^+$, $CD30^+$, $CD95^+$).

Для виявлення поверхневих структур лімфоцитів було використано метод прямої імунофлуоресценції, де флуоресцентна мітка була прикріплена до анти-CD моноклональних антитіл серії Leu фірми «Becton Dickinson» (США). Розрахунки проводили на лазерному миттєвому цитофотометрі фірми «Becton» (США).

Результати та обговорення. Найбільш позитивний вплив на параметри клітинного імунітету було виявлено у пацієнтів із псоріазом, яким призначали імунобіологічний препарат етанерцепт у поєднанні з вузькосмуговою (311 нм) фототерапією. Після лікування у цих пацієнтів завдяки значному зниженню продукції TNF та його концентрації в сироватці крові зменшилася вираженість прозапальних змін у клітинній ланці імунної системи, а також кількість лімфоцитів з маркером ранньої активації, який ініціює подальший каскад цитокінів та подовження запалення. Крім того, зменшення кількості $CD30^+$-лімфоцитів є непрямим показником, що свідчить про переключення відповіді Th2 (автоімунні прояви) на Th1, що своєю чергою забезпечує досягнення клінічної та імунологічної ремісії псоріатичного процесу. Надзвичайно важливим для функціонування імунної системи є зниження вмісту активованих лімфоцитів, які експресують Fas-рецептор, оскільки це призводить до збільшеного апоптозу лімфоцитів, зокрема Т-цитотоксичних лімфоцитів, а також до автоімунних і проліферативних змін, властивих загостренню псоріатичного процесу.

Висновки. Встановлено, що всі наші схеми лікування хворих на псоріаз мають імунореабілітуючі властивості, але ступінь їхньої вираженості був різним. Найефективнішою схемою лікування виявилось комбіноване застосування етанерцепту та УФБ-терапії, що дало змогу зменшити вираженість проліферативних та запальних змін у шкірі, знизити антигенне навантаження, рівень циркулюючих імунних комплексів, автосенсибілізацію та автоімунні порушення.

Ключові слова: псоріаз, системна імуносупресивна терапія, імунологічні зміни.

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