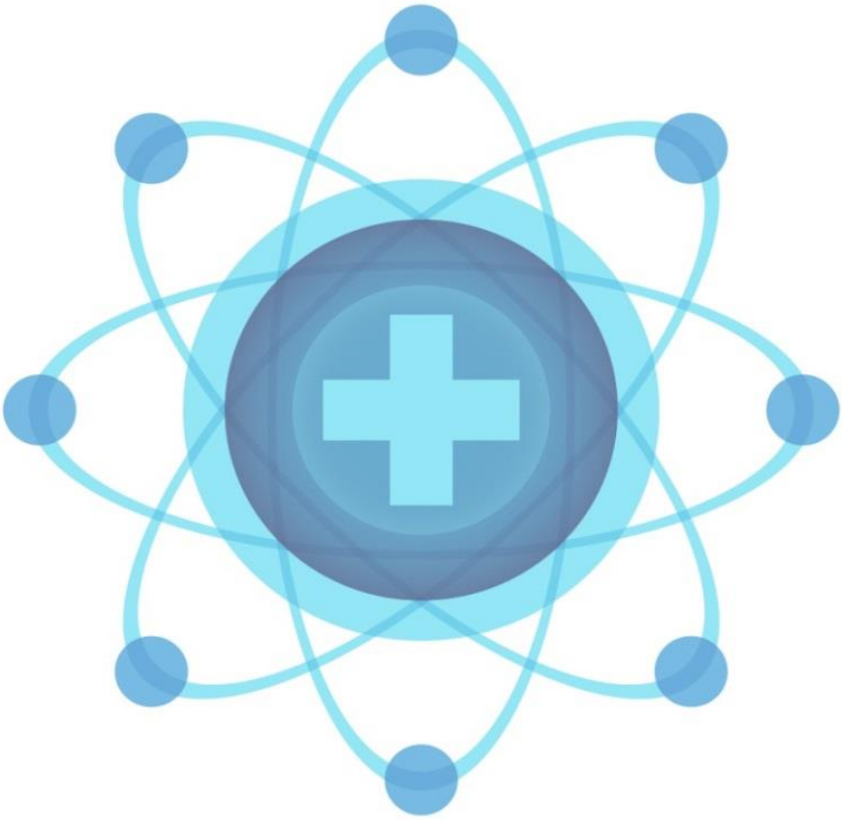

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MAIN MEANINGS OF IMMUNOLOGICAL DISORDERS IN PSORIATIC ARTHRITIS

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Abstract: The prevalence of psoriatic arthritis (PsA) in the general population is estimated at 0.3-1%, and psoriasis (PS) in the world is 2-3%, and the incidence of arthritis in patients with PS ranges from 5 to 42% [1]. According to modern researchers, the frequency of detection PsA at sick PS is 16-48% [2,3]. By data different authors incidence PsA is 3.6-6.0 on the 100000 population, a range prevalence ranges from 0.01 to 1.5% [3]. Despite the study of the prevalence, pathogenesis, clinic, diagnosis and therapy of PsA, there are still many poorly studied and debatable questions which require further research on this disease.

Keywords: psoriatic arthritis, psoriasis, immunological disorders.

Introduction. Psoriatic arthritis is a chronic, progressive systemic disease associated with psoriasis, with a predominant localization of the inflammatory process in the tissues of the musculoskeletal system. Particular interest in PsA is associated with an increase in the number of patients with this pathology and severe disabling consequences [4].

According to modern concepts, PsA is considered as a systemic autoimmune disease of a multifactorial nature. With this disease, there are violations of both cellular and humoral immunity. In PsA, as in other spondyloarthritis, various changes in the profile of pro- and anti-inflammatory cytokines are observed, which form a regulatory network and are involved in the pathogenetic mechanisms of this type of arthritis [4,5].

In PsA , HLA - B *27, HLA - B *38, HLA - C *06 are detected significantly more often than in patients with psoriasis and healthy individuals . A regular correlation has been found between the carriage of certain leukocyte antigens and the clinical manifestations of the disease [5,6]. HLA-B27 is closely associated with radiological signs of sacroiliitis, while HLA B38 and B39 are associated with peripheral arthritis, HLAB 27, B 39, and DQw 3 are associated with PsA progression [5].

In the pathogenesis of PsA, overproduction of circulating immune complexes containing immunoglobulin A (IgA) is of certain importance . In this disease, a

polyclonal gammopathy , the predominance of CD4 + T-lymphocytes in cellular synovial infiltrates was established. Lymphocytic infiltration is characteristic of psoriatic plaques, synovium, and enthesis . It has been established that in PsA there is an activation of the cellular response with the leading role of T-lymphocytes [6]. T-cell infiltrates of the skin and synovium consist mainly of CD8+ and CD4+T-lymphocytes (with a predominance of CD4+T-lymphocytes) in a ratio of 2:1, while in entheses and synovial fluid, the CD4:CD8 ratio is reversed [7]. These cells produce Th1-type cytokines, tumor necrosis factor-α, interleukin-2, and IFN-γ, which have pro- inflammatory activity [9].

In recent years, knowledge of immunopathogenesis has expanded. PsA . At PsA plays an important role in the imbalance of pro- and anti-inflammatory cytokines, such as TNF -α, IL-6, IL-1β, IL-12, IL-17, IL-23, and chemokines [8]. To date, IL-17 is a key cytokine in the pathogenesis of PsA . IL-17A induces keratinocytes to release other pro- inflammatory cytokines (IL-1β, TNF - α, IL-6). Cytokines formed in the skin, in turn, can have a direct or indirect effect on the development of PsA [10].

In these pathological conditions, there is an increase in the concentration of TNF -α in biological media and tissues of the body, in particular in the foci of psoriasis , synovial membrane, enthesis , synovial fluid and blood, which corresponds to the degree of activity of the inflammatory process [7,8].

Recent studies have established a relationship between individual genes of predisposition to psoriasis and PsA with the expression of individual cytokines. Thus, a significant association was shown between HLA-Cw6, which is usually detected in young patients with psoriasis and PsA, with TNF - α, as well as predisposition genes of the PSORS family located in loci 1, 3, 6 with TNF - α, IL -1 and IL -8. These data are of great interest and are a kind of "bridge" between the genetic and immunological concepts of psoriasis and PsA, as well as the key to the development of their gene correction [9,10].

Purpose of the study. Study of immunological disorders in psoriatic arthritis.

Material and research methods. We studied 125 patients with a reliable diagnosis of PsA (based on the CASPAR classification criteria proposed by the American Academy of Rheumatology in 2006). We determined the indicators of cellular, humoral and cytokine status in patients with PsA depending on the duration of the disease. The control group consisted of 20 healthy donors of comparable sex and age.

The state of the immune system was assessed by the expression of CD antigens - differentiation and activation markers. The following markers of immunocompetent cells were determined: CD 3+-, CD 4+-, CD 8+-, CD 20+-, CD 16+-lymphocytes. Expression of CD receptors was performed using monoclonal antibodies of the LT series . The determination of the concentration of immunoglobulins in the blood serum of the main three classes A, M and G was carried out by the generally accepted method of radial immunodiffusion according to Mancini Cytokines (TNF -α, IL - 6, IFN -γ) were determined in peripheral blood serum by enzyme-linked immunosorbent assay according to the instructions. The CEC concentration was

determined by selective precipitation in 4.16% PEG (polyethylene glycol) 6000 (Serva , Germany).

Research results.

In the results of our study, we determined the parameters of the cellular link of immunity depending on the duration of the course of PsA. At the same time, leukocytosis was observed in patients, more significant in patients with early PsA (9260±314 in 1 μl versus 7596±238 in 1 μl in the control group; p <0.01). In patients with late PsA, the average number of leukocytes was 8660±317 per 1 μl, which was significantly higher than in the control group (p <0.05).

A more accurate assessment of the content of T-lymphocytes is achieved by studying absolute indicators. Thus, in the peripheral blood of the control group, the content of T-lymphocytes was 1275±61.7 per 1 μl, which did not significantly differ from the indicators of patients with early PsA (1159±56.8 per 1 μl). However, in patients with long-term PsA , the level of CD 3+ cells significantly exceeded the control (1512.2±72.4 per 1 μl; p<0.05).

Helper activity in patients with the course of the disease for no more than 2 years was significantly reduced (p<0.05), and with a long course of the disease, an increase in the number of these cells up to 10 13.3 ± 31.8 in 1 μl was observed (p<0 .05). It is known that T-helpers are regulatory cells. CD 4+-lymphocytes, performing their helper function, help, firstly, B-cells to turn into an antibody - producing plasma cell; secondly, CD 8+-lymphocytes - into a mature cytotoxic T-cell; third, macrophages to carry out the effects of hypersensitivity. These functions of T-lymphocytes/helpers are realized due to the fact that they, in turn, are distributed into two subpopulations - Th 1- and Th 2-types, which perform different helper functions due to the production of different cytokines- interleukins .

The study of another immunoregulatory cell population - T- suppressors , capable of inhibiting too strong and too prolonged immunological reactions, i.e. regulating the strength and duration of the reaction to the antigen, showed that in the blood of patients with early PsA the absolute number of CD 8+ cells is 23.4% higher than the control (p<0.05), and with a long course of the disease - 28.1% lower (p<0.01) **(Table 1)** .

Table 1

The absolute number of T-cell immunity in patients with PsA in depending on the duration of the disease, (M ± m)

Index	Control, n=20	early PsA , n =28	late PsA , n = 36 _
Lake .	7596±238	9260±314***	8660±317**
Lymph. abs	2386±97.3	2275±83.7	2401±89.8
CD3+, abs	1275±61.7	1159±56.8	1512.2±72.4*
CD4+, abs	870.8±27.4	702.9±23.5***	1013.3±31.8**
CD8+, abs	577.4±19.2	677.9±25.4	420.2±31.6***

When analyzing the results of determining the values of T-lymphocytes in patients with PsA, the same direction of changes was revealed as with the absolute value. It should be noted that both low and high levels of T-lymphocytes serve as an unfavorable prognostic sign, indicating a chronic process.

subpopulation composition of T-lymphocytes was determined in patients . In patients with early PsA helper activity was reduced (31.2±1.3% versus 35.7±1.2% in control; $p<0.05$), and with a long course of the disease, a significant increase in the level of CD 4+ cells was observed, which averaged 43.1±1.4% ($p<0.05$).

Suppressor activity in patients with early PsA increased (28.9±1.3% versus 25.5±0.9% in control; $p<0.01$), and in patients with a long course of the disease, the number of CD 8+ cells was significantly reduced to an average of 16.8±0.7% ($p<0.01$).

The imbalance in the subpopulation composition of T-lymphocytes had an impact on the immunoregulation index , which in patients with early PsA was significantly lower than the control, and in patients with a long-term course of the disease it significantly increased ($p<0.001$), which indicated that the disease proceeds against the background of autoimmune aggression.

Comparative characteristics of the content of circulating CD20+ cells showed that in early PsA the level of these cells significantly increases, averaging 28.7±0.8% (in control - 21.4±0.7%; $p<0.01$). The maximum value of B-lymphocytes was observed in patients with long-term PsA - 34.8±1.2%, which is 1.72 times higher than the control ($p<0.001$) **(Table 2)** .

Table 2

Indicators of the humoral link of immunity in patients with different duration of PsA , (M ± m)

Index	Control, n=20	Early PsA , n = 30	Late PsA , n = 34
CD20+, %	21.4±0.7	28.7±0.8***	34.8 ± 1.2***
CD20+, abs	481.9 ± 18.2	671 ± 21***	835 ± 27***
IgG, g/l	11.3±0.67	16.1±0.78***	18.3 ± 1.15***
IgA, g/l	0.70 ± 0.013	1.13 ± 0.08***	1.12 ± 0.15**
IgM, g/l	1.61±0.051	1.8±0.15	1.7 ± 0.08

It should be noted that the analysis of the absolute values of B-lymphocytes revealed the same trend as with relative numbers. The absolute number of B-lymphocytes in patients with PsA was 1.6 times higher than in controls ($p<0.01$), with a long course of the disease it increased 1.81 times ($p<0.001$).

The level of IgG in PsA increased at its early stage (16.1±0.78 g/l vs. ±1.15 g/l, $p<0.01$). As for Ig A, its concentration significantly increased regardless of the

duration of the disease (p<0.05). A slight upward trend was found relative to the level of Ig M.

Increasing attention of researchers is attracted by a special class of immunocompetent cells that perform the killer function. We are talking about natural killer cells - NK cells (CD16+). In the control group, the content of natural killer cells (CD16+ cells) averaged 14.7±0.8% with individual fluctuations from 7 to 20%. The absolute value of this indicator averaged 350.7 ± 13.8 per 1 μl .

The relative content of NK cells in the bloodstream of patients with PsA at an early stage was 1.47 times higher than the control and averaged 21.6±1.0% (p<0.01). The absolute content of CD 16+-lymphocytes was 1.4 times higher than the control values - 491.4±15.6 per 1 μl (p<0.05). A different picture was observed at PsA with a long course. The level of killer activity was reduced by 1.77 times and averaged 8.3±0.5% (p<0.001). And the absolute value of CD16+ cells was 1.76 times lower than the control values - 199.2±8.3 in 1 μl (P<0.001) **(Table 3)** .

Table 3

Factors of nonspecific protection in patients with different duration of PsA , (M ± m)

Index	Control, n=20	Early PsA , n = 30	Late PsA , n = 34
CD16+%	14.7±0.8	21.6±1.0***	8.3±0.5***
CD16+, abs	350.7±13.8	491.4±15.6***	199.2±8.3***
CEC, cond. units	61.8±3.19	98.2±2.67***	114.0±3.17***

The imbalance of immunocompetent cells, the presence of hypersecretion of humoral protection cause the accumulation of abnormally high concentrations of CEC. The CEC level in PsA patients at an early stage was 1.58 times higher than the control (p<0.01). As the duration of the course of the disease increases, the concentration of the CEC increases even more to an average of 114.0±3.17 srv . units (p<0.001).

We also studied the levels of pro- inflammatory cytokines - TNF - α , IL-6 and IFN - γ in PsA patients with different duration of the disease **(table 4)**. As can be seen from our data, the level of TNF - α in patients with early PsA was 4.1 times higher than the control and averaged 97.3 ± 7.6 pg / ml (versus 23.9 ± 1.7 pg / ml in control; p<0.001). However, with a long course of this disease, an even greater increase in the synthesis of tumor necrosis factor-α is observed, the value of which averaged 120.7±12.3 pg /ml, which was 5 times higher than the control (p<0.001). It has been established that uncontrolled hyperproduction TNF - α underlies the chronicity of the immunopathological process and bone destruction.

The production of IL-6 in patients with PsA was significantly higher than in healthy individuals (63.4±17.1 pg /ml versus 21.5±1.6 pg /ml in the control group; P <0.001) with a maximum value in patients with a long course of PsA (85.3±15.4 pg /ml; p<0.001).

Table 4

The level of cytokines in patients with PsA depending on the duration of the disease , (M ± m)

Cytokines	Control, n=20	Early PsA , n = 30	Late PsA , n = 3 4
TNFα , pg /ml	23.9±1.7	97.3± 7.6 * **	120.7 ±12.3***
IL-6 , pg /ml	2 1 , 5 ± 1.6	6 3 , 4 ±17, 1 *	85 , 3 ±15, 4 * **
IFNγ , pg /ml	2 8 , 6 ± 2.1	77.2 ±4.8* **	8 1.6 ± 6.8 * ** _

Synthesis of IFN - γ correlates with the level of proliferation of keratinocytes and synovia during an acute attack in patients with PsA. This indicator in patients with an early course of the disease increased by 2.7 times compared to the control (up to 77.2±4.8 pg /ml 28.6±2.1 pg /ml; $p<0.001$). In patients with a longer course, the indices were even higher (81.6±6.8 pg /ml).

Thus, the study of the parameters of the immune system in patients with PsA revealed sharp multidirectional changes in the content of antibodies, the population composition of lymphocytes, which, in turn, affected the synthesis of pro-inflammatory cytokines. A chronic disruption in inflammatory signaling pathways likely leads to long-term changes in tissue immune cells of the skin and joints, which determine the severity of the characteristic clinical manifestations of the psoriatic process.

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