REVIEW ARTICLE

CONTENTS

The associations of cytokines and gens polymorphisms of β-adrenoceptors in patients with heart failure and some thyroid pathology (literature review and own observations)

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ABSTRACT

Aim: To analyze the role of cytokines in the progression of heart failure (HF) in patients with concomitant pathology of the thyroid gland.

Materials and Methods: The systematization of literature data on the role of cytokines in the progression of HF in patients with concomitant thyroid pathology (TP) was carried out. The results of our own research were presented.

Conclusions: The final chapter in the history of the role of cytokines in the progression of HF has not yet been written. Further studies, including genetic ones, are necessary. The patients with HF have higher levels of TNFβ and IL-6, and a lower concentration of IL-4, compared to the control group. Patients with a fatal outcome of the disease, in contrast to those who survived for two years, have an increased level of TNFβ. In patients with concomitant TP, who had repeated hospitalization, a lower level was registered, compared to that under conditions of a more favorable course of heart failure. Concentrations of cytokines in the blood of patients with HF are associated with gene polymorphisms of the β-adrenoreceptor system: the C-allele of the Gly389A polymorphism of the β1-adrenoceptor gene leads to a decrease in the risk of increasing TNFα; IL-1α increases in the presence of the A-allele of the Ser49Gly polymorphism of this gene. In patients with HF and concomitant thyroid pathology, the risk of IL-6 growth increases in homozygous (C) patients for the Ser275 polymorphism of the β3 subunit of the G-protein.

KEY WORDS: cytokines, polymorphism, thyroid gland, heart failure, genes, β-adrenoceptors

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INTRODUCTION

Cytokines (CN) and other inflammatory mediators may be associated with the development and progression of heart failure (HF) [1]. However, this path of pathogenesis remains insufficiently studied. The dynamics and influence of cytokines on the course of heart failure in patients with concomitant thyroid pathology also remain unclear.

AIM

The aim of this article is analyze of the role of cytokines in the progression of heart failure in patients with concomitant pathology of the thyroid gland.

MATERIALS AND METHODS

The narrative review represents an assessment of the most pertinent literary sources published in English language from 1990 to 2021, which dealt with the issues of dynamics and influence of cytokines (CN) on the course of heart failure (HF) in patients with concomitant thyroid pathology (TP). Also, the results of our own research were presented.

REVIEW AND DISCUSSION

The CN, synthesized mainly by leukocytes. This is where their other name comes from, such as interleukins (IL). They are also produced by mononuclear phagocytes and other cells of both the immune and other systems. It is a class of small peptides (8-30 kDa) that regulate intercellular and intersystemic interactions in the body, including stimulation or inhibition of cell growth, differentiation, functional activity and apoptosis, and also ensure the coordination of the action of the immune, endocrine and nervous systems under normal conditions and under diseases [1]. Interleukins are active in low concentrations. Their biological effect on cells is realized through interaction with specific receptors located on the cell membrane. The synthesis and secretion of interleukins is short-

term and strictly regulated. The spectra of biological activity of interleukins largely overlap: one process can be activated in a cell by more than one cytokine. In many cases, synergism is observed in the actions of interleukins. Interleukin and antigen are non-specific factors, so specific diagnosis of infectious, autoimmune and allergic diseases using cytokine level determination is impossible. But determining their concentration in the blood provides information about the functional activity of various types of immunocompetent cells, about the severity of the inflammatory process, its transition to the systemic level, and the prognosis of the disease [1].

Several studies have demonstrated increased expression and release of pro-inflammatory cytokines such as TNFα , IL-1, IL-6, IL-18, cardiotrophin-1 and Fas ligand, as well as several chemokines in patients with HF [2]. The levels of pro-inflammatory CN and chemokines in the plasma are most often increased, directly proportional to the worsening of HF according to NYHA and the decrease of the left ventricular eject fraction (LVEF). Increased expression of inflammatory mediators has been proven in the zone of acute myocardial necrosis (for example, adhesion molecules, TNF, IL-6-related other cytokines and chemokines) [3]. Some of these mediators provide predictive value that surpasses traditional risk markers in accuracy.

The pathogenetic role of pro-inflammatory CNS in HF was confirmed during research on various models of transgenic mice. Systemic administration of TNF to experimental animals in concentrations corresponding to those in the plasma of patients with HF, induces dilated cardiomyopathy [4-6]. Studies in genetically modified mice have also shown a link between the development of HF and IL-6, its receptor subunit glycoprotein (gp) 130, which is common to several CN in the IL-6 family, as well as various chemokines (eg, MCP- 1) and CXCL13 [4]. Proinflammatory CNS can modulate myocardial functions involving various mechanisms. Among them is stimulation of the development of hypertrophy and fibrosis by direct action on cardiomyocytes and fibroblasts, violation of the contractile ability of the myocardium due to a direct effect on intracellular Ca2+ transport and signal transmission through β-adrenoreceptors (β-AR), induction of apoptosis and activation of a number of genes in cardiomyocytes responsible for heart remodeling [5]. Inflammatory mediators may also have an indirect effect on the progression of HF by impairing bone marrow function with the development of secondary anemia; cause inadequate activation of endothelial cells and impairment of peripheral muscle function with induction of systemic inflammation .

During the acute phase of myocardial infarction (MI), CN production is, in fact, a response to damage. Triggers for the release of CN (such as TNFα , IL-6 and IL-1 α in MI, there is ischemia, reactive oxygen species formed in excess during ischemia-reperfusion cause membrane damage, and also stimulate the synthesis of molecular patterns associated with danger, which include ATP, uric acid, mitochondrial DNA, and heat shock proteins. This inflammatory process is a prerequisite for wound healing, scarring and the development of compensatory hypertrophy. Studies have also shown that these proinflammatory CN initiate a cardioprotective signaling cascade known as the "survival pathway" [6]. However, although a moderate cytokine response may be protective, an inappropriate and persistent inflammatory response may lead to the formation of a «maladaptive» situation. In addition, experiments with the participation of animals have demonstrated that with a large MI, the expression of CN genes can remain significantly elevated for a long time, especially in the non-infarcted zone. Levels of late activation of the CN correlate with LV SCD, which was demonstrated 20 weeks after MI in rats .

It remains an open question whether inflammatory processes can be involved in the pathogenesis of HF with preserved PV. Although increased inflammation is a well-known feature of HF with low LVEF, this process has not been sufficiently studied in diastolic HF. However, there are data showing that patients with diabetes and hypertension with signs of diastolic dysfunction, like patients with reduced PV, often have elevated TNF levelsα, IL-1β and IL-6 in the blood [7]. An important role has been proven T-cells in the remodeling of the myocardium, including an increase in the activity of the enzyme lysyl oxidase, which, due to changes in the properties of collagen, affects the increase in stiffness of the myocardium [8]. In mouse models of hypertension and metabolic syndrome, induction of a type I T-helper inflammatory phenotype (i.e., increased levels of TNFα , interferon-γ and IL-18) and an increased level of TFR, which potentially contributes to the development of myocardial fibrosis. In addition, it is known that the infusion of IL-6 in rats leads to concentric LV hypertrophy, an increase in the volume fraction of collagen, and an increase in myocardial stiffness [9]. It was shown that IL-18 increases the expression and production of osteopontin, which stimulates the formation of interstitial fibrosis , and TGF, which increases collagen synthesis and inhibits matrix degradation by reducing

MMP activity [10]. Increased production and decreased degradation of collagen and increased activation of lysyl oxidase-1, which determines the formation of insoluble collagen, can, in turn, eventually lead to LV diastolic dysfunction. These interactions may play a role in adverse myocardial remodeling in patients with HF and reduced LVEF. The results of studies concerning the levels of CNS in HF with preserved PV indicate a complex dysregulation of the cytokine network rather than a simple imbalance between the production of cytokines by T-helper types I and II. This may include increased production of mediators involved in both inflammation and fibrogenesis. Among them are galectin-3, increased activation of T-helpers, which implies hyperproduction of IL-6 and the development of myocardial fibrosis, and at the same time the lack of general regulation of the immune response due to a violation of the function of regulatory T-cells [11].

IL-4 is produced by immune cells, including CD4 + T-helper (Th) lymphocytes and mast cells. Among the many biological effects, the following should be highlighted: IL-4 in pathological processes contributes to the development of lung fibrosis [12], skin, and liver. Studies have shown a positive correlation between systemic IL-4 levels and fibrotic cardiac remodeling in both patients , as well as in animals in the experiment [13]. In addition, previous studies have established that mice of the Balb/c genetic line, which are characterized by a high level of circulating IL-4, have an increased deposition of collagen in the heart, an increase in the size of the LV and a decrease in AF (fibrous cardiomyopathy). Administration of IL-4 neutralizing antibodies significantly reduces cardiac fibrotic remodeling in C57BL/6 mice with coarctation of the aorta [14]. Vascular endotheliocytes express - IL-4 receptors. In the lungs, IL-4 activates endotheliocytes, inducing the production of endothelin-1, which leads to the development of pulmonary hypertension .

Myocardial fibrosis can lead to systolic dysfunction by several mechanisms, including disruption of force generation by myocytes, normal coordination of electromagnetic coupling, and asynchronous myocardial contraction. It was noted that after blocking IL-4 receptors, the development of fibrosis is slowed down and the contractility of the myocardium improves [14].

In the work of N. Peng et al. (2015) demonstrated that IL-4 is associated with an increase in the number of mast cells in the heart [15]. In pathological conditions, these cells can be activated by cytokines, in particular IL-4, which leads to increased secretion of a number of mediators responsible for the development of fibrosis [14]. Peng N. et al. (2015) also found a positive relationship between the functioning of mast cells and the formation of myocardial fibrosis [15].

Scientists from Poland demonstrated that human thyrocytes can themselves synthesize cytokines that activate T and B lymphocytes. The authors demonstrated that in patients with non-toxic goiter there is an increase in the concentration of IL-6 and IL-8 and other CN.

The only specific sign of autoimmune thyroiditis (AIT) is currently considered to be a certain set of morphological changes in the thyroid gland (TG). This gave reason to single out this disease as a separate nosology [16]. The pathogenesis of AIT is based on an autoimmune process, and it leads to partial or complete destruction of the thyroid gland with the development of characteristic morphological changes and secretory insufficiency.

Experimental AIT can be induced in mice by injection of murine Tr (mTg). The disease is characterized by lymphoid infiltration of the thyroid gland, increased production of mTg-specific antigens, and follicular destruction. Although the mechanisms by which CD4 + T cells cause the destruction of the thyroid gland in AIT are not fully understood, it is assumed that under these conditions the production of CNS by T-helper type I plays an important role. The combination of INF-γ and TNF-α produced by the thyroid gland, as well as an increase in the synthesis of INF-γ by lymphocytes, can contribute to the apoptosis of thyroid follicular cells due to the activation of caspases. The activity of AIT may increase after the introduction of IL-12. It is also known that the use of IL-4 can prevent the development of these manifestations [17].

There is an assumption that CNs play a certain role in the genesis of the syndrome of low triiodothyronine (SLT3). In particular, it is known that INF-α and IL-6 increase the risk of developing SLT3 in patients with acute MI and heart surgery [18]. Proinflammatory CN are often increased in SLT3 and are inversely correlated with the levels of thyroid hormones (TH) [19]. In addition, the CN are probably involved in the inhibition of the hypothalamic-pituitary axis, which is often observed in SLT3. This may be the second, after the action of local deiodinases (DY), explanation of the decrease in TRH mRNA production of the hypothalamus during SLT3. The relationship between pro-inflammatory CN and levels of TH was demonstrated in patients with obstructive pulmonary disease and diabetes [19].

Gullestad L. et al suggested that although "too many" of these mediators are maladaptive, "too few" of them may be harmful, illustrating the challenges

of immunomodulatory therapy in HF [20]. Given the central role of the FNPα in the pathogenesis of HF, therapeutic modulation targeting this interleukin has received particular attention. Taking into account the results of a number of studies, it was assumed that the inhibition of TNFα recombinant chimeric sTNFR2 (etanercept) may have a positive clinical effect in patients with HF . However, the Etanercept Worldwide (RENEWAL) randomized clinical trial was subsequently conducted to evaluate the effect of etanercept on morbidity and mortality in patients with HF. Based on the data analysis of 1,500 patients with HF symptoms and left ventricular ejection fraction (LVEF) ≥ 30%, it was established that there was no effect of the drug on mortality, hospitalization, or functional class dynamics [21]. The results of a sub-analysis of the study suggested a dose-outcome relationship, as there was a reduction in hospitalizations/deaths among patients receiving the lowest dose compared to those receiving the highest dose. Another series of studies focused on TNF was the ATTACH trial with a chimeric anti-TNF monoclonal antibody (infliximab) in 150 patients with HF, which was a placebo-controlled phase II trial in HF and LVEF 35%. This clinical trial was stopped at an early stage, because higher rates of mortality and hospitalization were registered in the active group with the use of high doses of the drug [22]. A possible explanation for this unfavorable result is that infliximab binds directly to the transmembrane form of TNF receptors, which ultimately leads to the induction of apoptosis of cardiomyocytes that present these receptors . Although such mechanisms may be useful in some diseases, such as inflammatory bowel diseases, however, they lead to the development of harmful effects in HF. On the other hand, it remains to be determined whether anti-TNF therapy can have a positive effect on HF with preserved LVEF, which is characterized by myocardial hypertrophy and fibrosis.

The failure of anti-TNF therapy has increased interest in a systemic approach to conducting immunomodulatory therapy in order not only to block the harmful effects of inflammatory cytokines, but also to increase the synthesis of anti-inflammatory CNS to restore the appropriate balance during the development of the inflammatory process. In a double-blind, placebo-controlled study, it was demonstrated that intravenous immunoglobulin (IVIg) increased LVEF by 5 units, while no significant changes were observed in the placebo group [23].

Neither immunosorption nor immunosorption was proven to have a positive effect in patients with HF, nor thalidomide [20], but not re-injection of autologous blood [24].

There is more and more evidence of the connection between two regulatory systems - the autonomic nervous system and the immune system [25]. Various studies have shown the presence of sympathetic innervation of lymphatic vessels, nodes and parenchyma of lymphoid organs [26]. At the same time, the immune response can alter the local and systemic adrenergic response. For example, intracerebroventricular administration of IL-1, IL-6, and TNF leads to activation of the central part of the sympathetic nervous system and an increase in norepinephrine metabolism. Peripheral introduction of INF-α or IL-1 causes a long-term increase in sympathetic tone at the level of spleen tissues. The role of such a feedback loop can be regulatory, affecting the specific form of the immune response. All subclasses of T-lymphocytes, with the exception of T-helper type 2, have β2-AR. Stimulation (β2-AR) plays an important role in the proliferation of CD4 + cells. Although the data are conflicting, most studies conclude that stimulation β2 -AR inhibits the proliferation of CD4 + T-lymphocytes [27]. This effect can be observed under conditions of increased levels of cAMP and protein kinase-A (PC-A) in T-lymphocytes [27]. This allows us to make an assumption that the inhibition of the proliferation of T cells β2-AR occurs through the cAMP / PK-A system. Stimulation β2-AR of mature cells in the process of activation leads to suppression of cellular immunity [27].

There is little research on the role β2-AR in the regulation of differentiation and function of B-lymphocytes [28]. Most of the research was done on mice. It was established that stimulation 2 -AR, among other factors, is accompanied by an increase in the formation of IgG 1 and IgM. At the same time, with a decrease in the concentration of HA in the blood plasma of immunodeficient mice and the simultaneous administration of immunized T-helper type 2 and B lymphocytes. It has been shown that insufficient stimulation β2 -AR leads to a significant decrease in the formation of IgG.

IL-4, produced by activated T-helper type 2, binds to its receptors (IL-4R) on the surface of B-lymphocytes to further regulate the formation of antibodies. Stimulation β2-AR of B-lymphocytes modulates this process by using several mechanisms. β2 - AR on activated B-lymphocytes through the cAMP / PC-A system increases the level of IgG 1 protein. In addition, stimulation β2-AR leads to increased expression of CD86 [29]. Activation β2 -AR is also accompanied by a decrease in the production of IL-12, changing the conditions favorable for the differentiation of type 1 T-lymphocytes. It is known that stimulation β2-

AR modulates the immune response, reducing the activity of cellular immunity regulation processes with the strengthening of the regulatory influence of the humoral link of immunity.

A connection between the decrease in density was established β2-adrenoceptors on B-lymphocytes and the presence of chronic rheumatic diseases . Stimulation β2-adrenergic receptors of neutrophils affects the chemotaxis of these cells, apoptosis and the release of a mediator [30]. In vitro studies have shown that stimulation β2 - adrenoceptors of monocytes reduces the formation of pro-inflammatory cytokines IL-1, TNFα, IL-6 and IL-8 by these cells [31]. With a 24-hour infusion of adrenaline 30 ng / kg / min, a decrease in the formation of TNF by monocytes is observed and increased synthesis of IL-10. The obtained data indicate an important role β2-AR in the modulation of the immune response.

Although there have been several studies in animal models demonstrating the anti-inflammatory effects of ACE inhibitors and β-adrenergic blockers, the effect of these immunomodulatory drugs in heart failure in humans appears to be quite modest. Despite the fact that high doses of enalapril significantly reduced the biological activity of IL-6 in heart failure with preserved left ventricular ejection fraction, this drug did not affect other pro-inflammatory cytokines. The influence of β-blockers on the development of inflammation in heart failure in humans is ambiguous and uncertain [32].

The study of the level of cytokines in patients with heart failure and comorbid thyroid pathology remains relevant. Associations of serum cytokine concentrations with gene polymorphisms of the β-adrenoceptor system are also insufficiently studied.

A series of experimental studies demonstrated that the biological effects of interleukins can explain some aspects of the pathogenesis of heart failure. The role of proinflammatory cytokines in HF has been confirmed by various models of transgenic mice. It is noteworthy that systemic administration of TNFα in concentrations comparable to those in the plasma of patients with HF provokes the development of dilated cardiomyopathy in animals [8]. Later studies in genetically modified mice also showed a relationship between IL-6 and its receptor subunit glycoprotein (gp) 130, which is common to several cytokines in the IL-6 family, as well as to various chemokines (eg, MCP-1) and CXCL13) and the development of HF [9]. Proinflammatory interleukins can modulate myocardial function through various mechanisms, including stimulation of hypertrophy and fibrosis by direct action on cardiomyocytes and fibroblasts, impairment of myocardial contractility by direct action on intracellular calcium transport, and signaling through β-AR, induction of apoptosis and stimulation of a number of genes in cardiomyocytes responsible for heart remodeling. Inflammatory mediators may also make a more indirect contribution to the progression of HF through bone marrow dysfunction with the development of secondary anemia, inadequate activation of endothelial cells, and peripheral muscle dysfunction with the secondary induction of systemic inflammation and reflex abnormalities inherent in heart failure [33].

In our study, it was established that patients with HF, compared to the control group, had higher levels of TNFα (by 38.8%, $p < 0.0001$), IL-6 (by 116.4%, $p < 0.0001$) and a lower concentration of IL-4 (by 27.3%, $p < 0.0001$), as well as a higher IL-1 ratioβ /IL-4 (by 37.9%, $p < 0.0001$) [34].

The function of TNF belongs to cellular signaling proteins (cytokines, phosphoproteins), participates in the processes of systemic inflammation, and is one of the cytokines that form the acute phase reaction. TNF is mainly produced by activated macrophages, to a lesser extent it is synthesized by other types of cells (T-helpers, NK-cells, neutrophils, mast cells, eosinophils). The main role of TNF is to regulate the interaction of immune cells, it triggers the process of apoptosis, causes cachexia, inflammation and inhibition of tumor growth, virus replication, regulates the production of pro-inflammatory IL1 and IL6 [35].

IL-1 (English Interleukin-1, IL-1) is a cytokine, a mediator of inflammation and immunity, synthesized by many cells of the body, primarily by activated macrophages, keratinocytes, B-lymphocytes and fibroblasts. Controls the activity of leukocytes, increases the number of bone marrow cells [1]. The existence of two similar interleukin-1s was also discovered:α and β [1].

IL-4 is synthesized by activated T-helper type 2 (Th2), mast cells and eosinophils. It regulates the growth and differentiation of B-lymphocytes, as well as the processes of biosynthesis and secretion of antibodies [36]. This IL affects the production and secretion of IgE and IgG 1 by B-lymphocytes, the switching of Th2 C-genes, the accumulation of eosinophils, the expression of low-affinity receptors for IgE CD23 on B-lymphocytes and mast cells. The cytokine prevents Th1 differentiation and their production of other ILs. IL-4 inhibits the proinflammatory activity of macrophages and their secretion of IL-1, FPN, and IL-6, i.e., ultimately has an anti-inflammatory effect [36].

IL-6 (eng. Interleukin-6, IL-6) – produced by activated macrophages and T-lymphocytes. Can act as

a pro-inflammatory and anti-inflammatory cytokine, stimulates the immune response [36].

According to the results of our study, it was established that patients with HF in combination with low triiodothyronine syndrome and thyroid pathology (TP) (diffuse goiter and autoimmune thyroiditis) probably have lower levels of IL-1β (by 21.9%, p = 0.03) and IL-4 (by 11.5%, p = 0.04), compared to patients without peripheral dysthyroidism syndrome. Patients without TP who died within two years of follow-up had higher levels of TNFα (by 29.2%, p = 0.01), and patients with the achievement of the combined end point (CC) (re-hospitalization due to heart failure decompensation and death) had a tendency to increase the content of IL-1β (by 16.6%, p = 0.05). In patients with HF and TP who had re-hospitalization (PG), the level of IL-4 was significantly lower (by 14.4%, p = 0.04), compared to patients with a favorable course of HF. A similar pattern was found in patients who had CCT (by 14.4%, p = 0.02) [34].

In the works of foreign authors, an increase in the expression and release of pro-inflammatory ILs, such as TNF, has been demonstrated α , IL-1, IL-6, IL-18, cardiotrophin-1 and Fas ligand, as well as several chemokines in patients with HF [9]. Concentrations of pro-inflammatory cytokines in plasma, most often elevated, are directly proportional to the worsening of PK according to NYHA and LVEF [9]. Moreover, some of these mediators have been found to provide prognostic information superior in accuracy to traditional risk markers .

During acute infections, hypoxia or tissue damage, monocytes are the main producers of IL and TNF, which, in turn, activate other links of the immune system . On the other hand, the increased activity of the sympatho-adrenal system, caused by the same factors, is an important regulatory mechanism that optimizes inflammatory reactions . Norepinephrine has been shown to have effects on innate immunity in vivo, including acting as a chemotactic agent for monocytes, as well as affecting TNF-α production . Prolonged or inappropriate stimulation of the sympathetic nervous system can lead to excessive inflammation or uncontrolled infection, leading to pathological effects including toxic shock and tissue damage [37].

The presence of expression of β-adrenoceptors in the ex vivo preparation of human mononuclear leukocytes has been proven [38]. It was demonstrated the expression of β1- and β2-AR subtypes on human monocytes, which caused an increase in the production of IL-1β upon simultaneous stimulation with catecholamines. Using selective antagonists β1 -AR, a pro-inflammatory response of monocytes was proved, which was functionally correlated with the generation of cAMP [38].

On number and activity β -AR and G-protein subunits are affected by the types of polymorphisms in the genes encoding them. This, in turn, can act at the level of interleukins produced by immunocompetent cells.

During the study, we established that in patients with HF, the C-allele of the Gly389A gene polymorphism β1-AR is associated with a decrease in the risk of increasing the serum level of TNF-α > 1.96 pg/ml (OR = 0.48 (0.25-0.93), p = 0.028 – dominant model of heredity; OR = 0.62 (0.39-0.99), p = 0.046 – log-additive model of heredity). In patients with HF with the A-allele of the Ser49Gly gene polymorphism β 1 -adrenoceptors, the level of IL-1 increases β > 2.13 pg/ml (OR 1.82 (1.01-3.27), p = 0.042 – dominant model of heredity). Heterozygous (according to A/G – Ser49Gly gene polymorphism β1-AR) patients with HF have a reduced risk of increasing the level of IL-6 > 2.13 pg/ml (OR 0.44 (0.21-0.93), p = 0.035 – overdominant model of heredity) [39].

We know that β-ARs are located on the membranes of both the endotheliocytes of thyroid vessels and on the cells of the parenchyma of the gland. There are data that the activity of deiodinases (both peripheral and thyroid) may also depend on polymorphisms β-AR. In turn, it should be noted that thyrocytes can produce IL locally. In the genesis of the development of TP, both genetic and inflammatory factors play a role.

We found that patients with HF and TP who have the heterozygous genotype of the Ser49Gly polymorphism (c,145A>G) of the β 1 -AR gene have an increased risk of increasing the level of TNF-α (OR = 4.55 (1.27-16.34), p = 0.028). The risk of increased IL-6 level increases in homozygous (C / C) patients for the Ser275 polymorphism of the gene of GNβ3 in the presence of TP (OR = 5.86 (1.81-19.0), p = 0.003) [39].

In vitro studies have shown that homozygotes for Ser49 (AA genotype) have a lower functional activity of adenylate cyclase compared to carriers of the G allele, but are more sensitive to adrenaline stimulation [40]. Another study found no differences in basal adenylate cyclase activity, but confirmed high sensitivity to long-term agonist exposure. It is possible to assume that the G allele does β1 -AR is less sensitive to adrenal stimulation [40].

We found that the risk of increasing the level of IL-6 increases in homozygous (C / C) patients for the Ser275 polymorphism of the gene of GNβ3 in the presence of TP (OR = 5.86 (1.81-19.0), p = 0.003) [37].

CONCLUSIONS

In conclusion, it should be noted that the final chapter in the history of the importance of cytokines in the formation and progression of heart failure, especially in patients with concomitant pathology, has not yet been written. Further studies, including genetic ones, are needed.

In our studies, it was established that patients with heart failure have higher levels of TNFα (by 38.8%) and IL-6 (by 116.4%), a lower concentration of IL-4 (by 27.3%) compared to the control group. Patients with a fatal outcome, unlike those who survived for two years, had an increased level of TNFα (by 29.2%). A lower IL-4 level (by 14.4%) was registered in patients with concomitant thyroid pathology who were re-hospitalized, compared to those with a more favorable course of heart failure. Concentrations of cytokines in the blood of patients with heart failure are associated with gene polymorphisms of the β-adrenoreceptor system: the C-allele of the Gly389A polymorphism of the β 1 -adrenoceptor gene leads to a decrease in the risk of TNFα elevation (OR = 0.48, dominant model); IL-1α increases in the presence of the A-allele of the Ser49Gly polymorphism of this gene (OR = 1.82, dominant model). In patients with heart failure and concomitant thyroid pathology, the risk of increasing IL-6 increases in homozygous (C) patients for the Ser275 polymorphism of the β 3 subunit of the G-protein (OR = 5.86).

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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