DOI: 10.20514/2226-6704-2022-12-6-422-429
EDN: HBWFZP
УДК [616-002-02:577.175.14]:616.12-008.46-07

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ИНТЕРЛЕЙКИН-1 — БИОЛОГИЧЕСКИЙ МАРКЕР ПРИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ

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Interleukin-1 is a Biological Marker in Heart Failure

Резюме

Воспаление является универсальной реакцией живого организма на различные повреждающие факторы и направлено на восстановление целостности тканей и минимизацию гибели клеток. Активными участниками воспалительного ответа являются провоспалительные цитокины, в частности интерлейкины. У пациентов с сердечной недостаточностью воспалительные реакции приводят к повреждению кардиомиоцитов, их апоптозу и активации нейрогуморальных систем, которые способствуют запуску гибернации миокарда и механизмов его ремоделирования. Цель представленного обзора — рассмотреть интерлейкин-1 (IL-1) качестве диагностического и прогностического маркера при сердечной недостаточности, а также влияние лечения рекомбинантной формой IL-1R на течение заболевания.

Ключевые слова: *воспаление, биологический маркер, сердечная недостаточность, цитокины, интерлейкины, анакинра*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

Статья получена 06.11.2021 г.
Принята к публикации 14.07.2022 г.

Для цитирования: Алиева А.М., Кисляков В.А., Воронкова К.В. и др. ИНТЕРЛЕЙКИН-1 — БИОЛОГИЧЕСКИЙ МАРКЕР ПРИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ. Архивъ внутренней медицины. 2022; 12(6): 422-429. DOI: 10.20514/2226-6704-2022-12-6-422-429. EDN: HBWFZP

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Abstract

Inflammation is a universal response of a living organism to various damaging factors and is aimed at restoring tissue integrity and minimizing cell death. Proinflammatory cytokines, in particular interleukins, are active participants in the inflammatory response. In patients with heart failure, inflammatory reactions lead to damage to cardiomyocytes, their apoptosis and activation of neurohumoral systems, which contribute to the initiation of myocardial hibernation and mechanisms of its remodeling. The purpose of this review is to consider IL-1 as a diagnostic and prognostic marker in heart failure, as well as the effect of treatment with a recombinant form of IL-1R on the course of the disease.

Key words: *inflammation, biological marker, heart failure, cytokines, interleukins, anakinra*

Conflict of interests

The authors declare no conflict of interests

Sources of funding

The authors declare no funding for this study

Article received on 06.11.2022

Accepted for publication on 14.07.2022

For citation: Alieva A.M., Kislyakov V.A., Voronkova K.V. et al. Interleukin-1 is a Biological Marker in Heart Failure. The Russian Archives of Internal Medicine. 2022; 12(6): 422-429. DOI: 10.20514/2226-6704-2022-12-6-422-429. EDN: HBWFZP

Introduction

As of today, the mortality due to chronic heart failure (CHF) still remains at very high level [1]. According to the large-scale epidemiological protocol EPOCA, the risk of total mortality due to heart failure (HF) exceeds the risk of total mortality in individuals without CHF by more than 10 times, and the average life expectancy in patients with CHF of functional class I–II and III–IV FC (according to the New York Heart Association (NYHA) CHF severity classification) is 7.8 and 4.8 years, respectively [2]. According to the European registry of EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot), mortality in patients with CHF of FC I–II and III–IV was 4.8 % and 13.5 % within one year, respectively [3]. According to the present-day literature sources, survival in CHF is often worse than in malignant tumors [4]. The results of many studies have demonstrated that five-year survival rate after HF diagnosing is about 25–50 % [3].

The search for new biological markers and analysis of the pathophysiological role and changes in their levels under various treatment options allowed understanding many pathogenetic aspects of the development and course of CHF [4]. Over the past twenty to thirty years, significant progress was achieved in the investigation of cardiovascular biomarkers. Determining the concentration of natriuretic peptides (NUP) that were used as biomarkers for the diagnostic and prognostic evaluation of patients with CHF and its implementation in the foreign and Russian clinical practice caused fundamental changes [5]. Currently, the assessment of the level of brain NLP (BNP) and its N-terminal precursor (NT-proBNP) is a kind of "gold standard" for diagnosing HF and predicting its course, however, limitations due to the impact of many factors on the level of these biomarkers, the ambiguity of threshold values, and sufficiently low information content in cases of CHF with preserved left ventricular ejection fraction (LVEF) necessitate further scientific and clinical trials aimed at developing more sensitive and specific laboratory tests [1, 5]. The new biological markers such as copeptin, adrenomedullin, galectin-3 (Gal-3), stimulating growth factor ST2, chemokine CX3CL1, fractalkine, etc., are getting all the closer to being implemented into biomedical practice [6=8].

Inflammation is a common response of a living organism to various damaging factors and is aimed at restoring tissue integrity and minimizing cell death. Initially, oxidized products and proteins of damaged extracellular matrix are released from the damaged or dead cells; they are recognized by sentinel toll-like receptors (TLRs), resulting in the activation of pro-inflammatory response. An active role in inflammatory response is played by pro-inflammatory cytokines (CKs), particularly, interleukins (ILs), tumor necrosis factor-α (TNF-α), chemokines and their receptors, cell adhesion molecules (integrins, selectins, etc.), as well as the acute-phase proteins (C-reactive protein (CRP) and pentraxin 3 (PTX3)). The impact of pro-inflammatory CKs leads to the activation of fibroblasts and cardiac tissue cells in the area of inflammation. Activated cells start producing CKs and growth factors that are potent chemoattractants and play a significant role in enhancing the inflammatory response. Neutrophils and monocytes secrete transforming growth factor-β (TGF-beta), including growth differentiation factor-15 (GDF-15) that attenuates macrophage response and protease production. In the patients with HF, inflammatory reactions result in the damage to cardiomyocytes, their apoptosis, and activation of neurohumoral systems that trigger myocardial hibernation and the mechanisms of its remodeling [9]. The features of inflammatory response in each specific case depend on the interaction of pro-inflammatory and anti-inflammatory CKs [9].

The objective of this review was to consider IL-1 as a diagnostic and prognostic marker in HF, as well as to analyze the impact of treatment with a natural recombinant IL-1R on the course of the disease.

Sourcing methodology

This paper provides the review of relevant publications. The analysis of literature sources was carried out using PubMed, RSCI, MedLine, Google Scholar, Science Direct databases. The authors reviewed both foreign and Russian papers. The search was carried out using the following keywords: biomarkers, heart failure, interleukin-1. This review mainly includes the description of studies conducted over the past 10 years, as well as selected fundamental sources written earlier.

Interleukin-1: structure and physiological functions

Understanding the role of IL-1 in the pathogenesis of inflammation significantly improved after the publication of the paper "Biologic basis for interleukin-1 in diseases" [10]. Blocking IL-1β is currently the standard of care in autoinflammatory diseases [11]. Autoinflammatory conditions often respond to IL-1β blockade, and are much less sensitive to immunosuppressive therapy [11].

The IL-1 family includes 11 CKs and 10 receptors; IL-1β and IL-18 are the best investigated ones [10, 12]. The description of these 11 members, their receptors, co-receptors and their important functions are presented in the Table. There are 4 CKs with anti-inflammatory effect, among these, IL-1Ra (IL-1 receptor antagonist) and IL-36Ra (IL-36 receptor antagonist) are specific, whereas IL37 and IL-38 are nonspecific [13]. The recombinant form of naturally occurring IL-1Ra is anakinra. Anakinra, as already mentioned, is used to treat a wide range of inflammatory conditions, including cardiovascular diseases (CVDs) [14]. IL-36Ra, IL-37, and IL-38 are not currently approved for human use, however, the results of preclinical studies revealed several indications for the management of human autoimmune diseases [15]. Alongside with the anti-inflammatory members of the IL-1 family, extracellular domains called "soluble receptors" also suppress inflammation. For example, soluble IL-1R2 neutralizes IL-1β, and IL-18BP (IL-18 binding protein) neutralizes IL-18 (Table) [16].

Il-1β synthesis and secretion

IL-1β binds to IL-1 type 1 receptor (IL-1R1); then a co-receptor chain, an additional protein (IL-1RAcP), is assembled [13]. This ternary complex recruits the adapter protein MyD88 (myeloid differentiation primary response gene 88) to the Toll-IL-1 receptor (TIR) domain of each receptor. Subsequently, phosphorylation of a part of the kinases occurs; the nuclear factor-κB (nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)) moves into nucleus, and transcription of pro-ILβ occurs [17]. Another "key player" is inflammasome, a cytosolic molecular structure that includes an adaptor protein, procaspase 1, and a sensor molecule. The most well-described inflammasome has a sensor molecule called a nucleotide-binding domain, and a leucine-rich repeat pyrine domain (NLRP3). This sensory molecule can be activated by both infectious stimuli known as pathogen-associated molecular patterns (PAMPs) and non-infectious ones in the form of damage-associated molecular patterns (DAMPs) (cholesterol, amyloid beta, urate crystals, and many others) [13]. This activation is due either to the binding of adenosine phosphate (ATP) to P2X7 receptor and the outflow of potassium into extracellular space, or the production of reactive oxygen species (ROS). After activation of the NLRP3 inflammasome, procaspase 1 turns into an active enzyme [17]. Then, active caspase 1 cleaves the IL-1 precursor in secretory lysosomes or in cytosol followed by the secretion of "mature" IL-1β [18].

Table. *Members of IL-1 family. Adapted from 1. Dinarello C.A. Overview of the IL-1 family in innate inflammation and acquired immunity. Immunol Rev. 2018; 281:8–27. DOI: 10.1111/imr.12621. [12].*

IL-1 family	Receptor	Coreceptor	Property
IL-1α, IL-1β	IL-1R1	IL-1R3	Proinflammatory
IL-1Receptor Antagonist	IL-1R1	NA	Anti-inflammatory
IL-18	IL-1R5	IL-1R7	Proinflammatory
IL-33	IL-1R4	IL-1R3	Провоспалительная/ Proinflammatory
IL-36 α, β, γ	IL-1R6	IL-1R3	Proinflammatory
IL-36 Receptor Antagonist	IL-1R6	NA	Anti-inflammatory
IL-37	IL-1R5	IL-1R8	Anti-inflammatory
IL-38	IL-1R6	IL-1R9	Anti-inflammatory

IL-1 and heart failure

It was proved that patients with HF have significantly increased levels of various pro-inflammatory CKs, including IL-1 [10, 11]. The inflammatory marker CRP, a known surrogate marker of IL-1 activity, is an independent predictor of adverse outcomes in the patients with acute HF (AHF) and CHF [19]. The cytokine hypothesis of HF suggests that a triggering event induces the activation of pro-inflammatory CKs leading to their negative impact on LV function and to the acceleration of HF progression [11].

Several mechanisms were found to form a correlation between IL-1 concentrations and impaired LV systolic function. IL-1β is proven to reduce the beta-adrenergic response of L-type calcium channels through a cyclic adenosine monophosphate-independent mechanism [20]. Moreover, IL-1β reduces the expression of genes involved in the regulation of calcium homeostasis [21]. IL-1β increases the expression of nitric oxide synthase (NOS) in cardiac myocytes; it leads to increased nitric oxide (NO) activity and decreased myocardial contractility [22].

Several members of the IL-1 family have beneficial effects on myocardium. Two members, IL-33 and ST2, are a ligand and a receptor, and have cardioprotective properties. Two main isoforms of ST2 were identified: ST2L transmembrane receptor and soluble sST2 receptor. Soluble ST2 blocks the protective action of IL-33 contributing to the development of remodeling and fibrosis processes. ST2/IL-33 signaling system is involved in the regulation of inflammatory, neurohormonal activation and prevention of cardiac remodeling [23]. Increased sST2 expression was registered in patients with myocardial hypertrophy, fibrosis, dilatation of cardiac chambers, and reduced ventricular contractility, and is considered to be an independent predictor of one-year mortality in AHF [24]. Besides, it is proven to be a significant predictor of hospitalizations and mortality in stable CHF patients [25]. The patients with elevated sST2, as a rule, have increased LV volumes, reduced LV contractility, and elevated pulmonary artery pressure according to echocardiography (ECHO CG). The individuals with CHF demonstrated better hemodynamic parameters at sST2 concentrations below 35 ng/mL. As a result, the investigators assumed that during the outpatient treatment of patients with HF, this blood sST2 level can be used to monitor the effectiveness of treatment [26].

Healthy mice demonstrated reversible systolic LV dysfunction and decreased LV contractility reserve (measured by the decreased response to isoproterenol) after both single and multiple injections of IL-1β [27]. To investigate the effect of circulating IL-1 activity, mice received injections of plasma obtained from patients with AHF, patients with chronic systolic HF, as well as from healthy volunteers. The results were similar to the exogenous administration of IL-1β as described above: plasma of decompensated HF patients caused significant systolic and diastolic LV dysfunction and decreased cardiac contractility. It is of interest that mice pretreated with anakinra or IL-1β antibody did not show this negative effect [28]; this fact leads to the suggestion that IL-1β has cardiodepressive properties. Rodents injected with plasma from patients with stable systolic HF and elevated CRP levels had normal systolic heart function at rest along with the significantly deteriorated contractile reserve [28].

The experimental study performed in 2010 in the field of cardio-oncology by Zhu J. et al. [29] using rodents demonstrated that IL-1 mediates the cardiotoxicity of doxorubicin. A sequential trial confirmed that blocking IL-1 with anakinra reduced doxorubicin-induced microstructural damage to cardiac tissue and improved LV ejection fraction (LVEF) [29]. Similar data were obtained in the study of radiation-induced cardiopathy in mice and the effect of anakinra on it [30].

First clinical study to evaluate the effect of IL-1 blockade on cardiac function revealed that a single injection of anakinra (150 mg) in patients with rheumatoid arthritis (RA) and without HF significantly improved the parameters of myocardial contractility and relaxation, coronary flow reserve, and endothelial function [31]. American physicians provided data on a female patient with RA and HF with preserved EF (HFpEF) who demonstrated an improvement in NYHA FC and peak aerobic capacity after switching from etanercept (a TNF-α inhibitor) to anakinra; this fact also indicates a positive effect of IL-1 blockade on HF course [32].

A double-blind, randomized, placebo-controlled, cross-over D-HART study was aimed to determine the effects of anakinra IL-1 blockade on aerobic exercise capacity in 12 patients with preserved LVEF and CRP level >2 mg. Anakinra resulted in a statistically significant improvement in maximal oxygen consumption (+1.2 mL/kg/min, $p = 0.009$) and a significant decrease in plasma CRP levels (−74 %, $p = 0.006$). Decreased CRP concentrations correlated with an improvement in maximal oxygen consumption ($r = −0.60$, $p = 0.002$). IL-1 blockade with anakinra during 14 days significantly reduced the systemic inflammatory response and improved aerobic exercise capacity in patients with HFpEF and elevated plasma CRP levels [33].

ADHF study (A Randomized, Double-Blinded, Placebo-Controlled Pilot Study) included 30 patients with AHF, decreased LVEF (40 %), and elevated CRP (≥5 mg/l), who were treated with anakinra or placebo. After 72 hours, anakinra reduced CRP by 61 % from baseline compared with a 6 % reduction in the placebo group ($p = 0.004$). After 2 weeks, patients treated with anakinra demonstrated an increase in LVEF [+10 % (+3, +14)] compared with the placebo group (0 (−16 % to +5 %), $p = 0.020$). The authors summarized that IL-1 blockade with anakinra reduces systemic inflammatory response in patients with AHF [34].

The objective of the study conducted by Imen T. et al. in 2017 was analysis of the correlation between IL-1β-31T/C polymorphism and serum IL-1β levels and the risk of developing AHF in 320 patients with dyspnea (160 with AHF and 160 without AHF) and in 100 healthy volunteers. Genotyping of IL-1β was performed using restriction fragment length polymorphism. IL-1β concentration was significantly higher in patients with HF compared with the group without HF and with the control group. Results of the distribution of IL-1β-31T/C genotypes and allele frequencies revealed no significant difference between three groups. Serum levels of IL-1β were found to be higher in cases of TT genotype than in TC and CC ones [35].

The prognostic stratification of patients with idiopathic dilated cardiomyopathy (DCM) is known to be a complicated task. In 2017, Italian scientists have studied the additive significance of assessing biomarkers of inflammasome activation and systemic inflammation in order to further stratify long-term risk in patients with DCM. 156 outpatients with DCM were examined (mean age 58 years, 77 % males, median LVEF 35 %, mean serum sodium 139 meq/L, BNP median 189 pg/mL, median IL-1 beta (Il-1β) 1.08 pg/mL, median IL-6 1.7 pg/mL, and median IL-10 2.7 pg/mL). During the follow-up period of 89.6 months, 35 patients (22 %) died/underwent heart transplantation. Patients who died/underwent heart transplantation were more likely to have NYHA class III, had atrial fibrillation (AF), lower LVEF, and higher BNP concentrations. Levels of IL-1β, IL-6 and IL-10 did not differ significantly between the groups of patients with good or poor prognosis. There were no significant differences in IL-1β values among either different NYHA classes or LVEF quartiles. However, in a multidimensional model, IL-1β was a strong and independent predictor of all-cause mortality (HR 1.193, 95 % CI 1.056–1.349, p = 0.005 for log-squared values). Other factors associated with poor outcome included: male sex, presence of AF and blood sodium level. The estimated time-dependent ROC curve of multivariate model is AUC 0.74 (95 % CI 0.65–0.86) [36].

In 2017, Tassell B. et al. suggested that the administration of an IL-1 receptor antagonist could suppress inflammatory response and improve peak aerobic exercise capacity in patients with decompensated systolic HF. In the REDHART (Recently Decompensated Heart Failure Anakinra Response Trial) clinical protocol, 60 patients with reduced LVEF (<50 %) and elevated CRP levels (>2 mg/L) were examined. Eight patients withdrew from the study on their own volition. Patients were randomized in three groups: group 1 (16 individuals) 14 days after the discharge from the hospital received anakinra s/c at a dose of 100 mg for 2 weeks, group 2 (18 individuals) received anakinra injections at a dose of 100 mg up to 12 weeks, and group 3 (18 individuals) received placebo. Patients were monitored for maximal oxygen consumption (Vo2, mL/kg per minute) and ventilation efficiency (VE/Vco2 slope indicates the relationship between ventilation and CO2 production). Anakinra therapy had no effect on maximal Vo2 (Vo2 peak) or VE/Vco2 slope in 2 weeks. After 12 weeks, patients who continued anakinra demonstrated an improvement in Vo2 peak from 14.5 (10.5–16.6) mL/kg per minute to 16.1 (13.2–18.6) mL/kg per minute (p = 0.009 for intergroup variations). The rate of death or readmission for HF in 24 weeks was 6 %, 31 %, and 30 % in the patients who received anakinra for 12 weeks, for 14 days, and in placebo group. Larger extension studies are required to confirm the effect of the long-term treatment with the studied agent on maximal Vo2 and readmission for HF [37].

Aerobic capacity, as measured by Vo2, is one of the most powerful predictors of HF prognosis. Inflammation is a key factor that contributes to the change in aerobic capacity, and IL-1 is known to be involved in this process. Apoptosis-associated speck-like protein (ASC) containing a CARD domain is required for the activation of IL-1β and IL-18 inflammasomes. ASC expression is controlled by epigenetic modification; lower ASC methylation is associated with worse outcomes in HF. All this information determined the need for a trial to analyze the relationship between methylation of ASC, IL-1β and IL-18 with Vo2 peak in patients with HF. This study was conducted in North America by the staff of the Department of Cardiology at the University of Alabama, the Department of Cardiology at Stony Brook University, and Emory University. In this paper the relationship between ASC methylation, IL-1β, IL-18, and Vo2 peak was analyzed in 54 stable outpatients with HF. All participants had HF of NYHA FC II and III and were able to complete a treadmill exercise test. Results obtained: mean Vo2 peak was 16.68 ± 4.7 mL/kg/min, Vo2 peak was positively correlated with the average percentage of ASC methylation (r = 0.47, p = 0.001) and negatively associated with IL-1β (r = −0.38, p = 0.007); multiple linear regression models demonstrated that Vo2 peak increased by 2.30 mL/kg/min for every 1 % increase in ASC methylation and decreased by 1.91 mL/kg/min for every 1 pg/mL increase in plasma IL-1β [38].

In 2019, a study was conducted with the objective of analyzing the relationship between IL-1β and sST2 and the prognostic value of the combination of these biomarkers in patients with AHF. As part of the clinical protocol, 316 patients hospitalized with AHF were examined sequentially (age 72 ± 12 years, 57 % males, LVEF 45 ± 17 %). IL-1β concentration on admission was associated with previous hospitalizations for HF, more severe HF, higher concentrations of NT-proBNP and high-sensitivity troponin T. IL-1β levels were higher in patients who died within a year of hospitalization (n = 52, 16.5 %) (p = 0.005). Circulating IL-1β demonstrated positive correlation with sST2 (ρ = 0.65; p < 0.001). Patients with high sST2 and Il-1β levels had a significantly higher risk of death (30 % vs 14 %; hazard ratio: 2.52; 95 % confidence interval: 1.40–4.56; p = 0.002) [39].

In 2021, American investigators evaluated the effect of IL-1 blockade on cardiac remodeling. Transverse narrowing of the aorta was performed in C57BL laboratory mice. Six weeks after the intervention, the progressive decrease in EF and the increase in LV mass and size were reduced after intraperitoneal administration of an IL-1 receptor antagonist (IL-1ra). IL-1ra reduced the expression of collagen-1, tissue inhibitor of metalloproteinases-1 (TIMP1), and periostin. Infiltration of immune cells (macrophages and lymphocytes) was also reduced in mice treated with IL-1ra. In addition, decreased concentrations of cytokines IL-1, IL-18, and IL-6 was observed after the administration of IL-1ra [40].

In the same year, a pooled analysis of three early-phase randomized clinical trials was performed. Endpoints included the pool of all-cause deaths and new-onset HF, and the pool of all-cause deaths and HF hospitalizations during follow-up in one year. The safety of anakinra was also analyzed, including injection site reactions and serious infections. This study included 139 patients with ST-elevation myocardial infarction (STEMI) from three single studies: VCUART (n = 10), VCUART2 (n = 30), and VCUART3 (n = 99). 84 (60 %) individuals of these patients were randomized to anakinra group and 55 (40 %) to placebo group. Treatment with anakinra significantly reduced the incidence of all-cause death or worsening HF (7 (8.2 %) vs 16 (29.1 %), log P = 0.002) and all-cause death or hospitalization for HF (0 (0) vs 5 (9.1 %), log-rank P = 0.007). Patients treated with anakinra had significantly more pronounced injection site reactions (19 (22.6 %) vs 3 (5.5 %), p = 0.016) with no significant difference in the incidence of serious infectious complications (11 (13.1 %) vs 7 (12.7 %), p = 0.435). Treatment with anakinra significantly reduced the area under the curve for highly sensitive CRP from baseline to 14 days (75.48 (41.7–147.47) vs. 222.82 (222.82 (117.22–399.28) mg/day/L, p < 0.001). The researchers concluded that IL-1 blockade with anakinra for 14 days in patients with STEMI reduces the rate of new-onset HF or of hospitalizations for HF after 1 year [41].

The D-HART 2 study is a randomized, double-blind, placebo-controlled, single-center, phase 2, 2:1 clinical trial that included patients with HFpEF, NYHA FC II–III, and with highly sensitive CRP levels >2 mg/L. Patients received anakinra 100 mg once daily or placebo during 12 weeks. The primary endpoints included changes in maximal oxygen consumption and ventilatory capacity at week 12; secondary endpoints were the effects of IL-1 blockade on cardiac performance, systemic inflammation, endothelial function, life quality, nutritional status, and clinical outcomes. This study is completed and its results are upcoming [42].

Conclusion

Currently, there are state-of-the-art technologies for identification of new biological markers, therefore, it would be reasonable to develop a multibiomarker model for diagnosing and predicting the CVDs course. This will definitely require the improvement of bioinformational technologies used for a large database analysis. This literature review indicates the potentially important diagnostic and prognostic value of interleukin-1 assessment. The further scientific and clinical trials are expected to demonstrate the possibility of its use as an additional laboratory method for the diagnosis, risk stratification and prediction of cardiovascular events in the patients with HF. The effect of interleukin-1 blockade on reducing morbidity and mortality in CHF is to be assessed in more detail, of course, taking into consideration the reasonable costs and side effects of the drugs.

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Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

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Список литературы/Referents:

1. Tsao C.W., Lyass A., Enserro D. et al. Temporal trends in the incidence of and mortality associated with heart failure with preserved and reduced ejection fraction. JACC: heart failure. 2018; 6(8): 678-685. DOI: 10.1016/j. jchf.2018.03.006.
2. Фомин И.В. Хроническая сердечная недостаточность в Российской Федерации: что сегодня мы знаем и что должны делать. Российский кардиологический журнал. 2016; (8):7-13. DOI: 10.15829/1560-4071-2016-8-7-13.
   Fomin I.V. Chronic heart failure in the Russian Federation: what we know today and what we must do. Russian journal of cardiology. 2016; (8):7-13. DOI: 10.15829/1560-4071-2016-8-7-13 [in Russian].
3. Maggioni A.P., Dahlström U., Filippatos G. et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). European journal of heart failure. 2013;15(7) :808-817. DOI: 10.1093/eurjhf/hft050.
4. Алиева А.М., Резник Е.В., Гасанова Э.Т. и др. Клиническое значение определения биомаркеров крови у пациентов с хронической сердечной недостаточностью. Архивъ внутренней медицины. 2018; 8(5):333-345. DOI: 10.20514/2226-6704-2018-8-5-333-345.
   Alieva A.M., Reznik E.V., Hasanova E.T. et al. Clinical significance of the determination of blood biomarkers in patients with chronic heart failure. Archive of Internal Medicine. 2018; 8(5):333-345. DOI: 10.20514 / 2226-6704-2018-8-5-333-345 [in Russian].
5. Гаспарян А.Ж., Шлевков Н.Б., Скворцов А.А. Возможности современных биомаркеров для оценки риска развития желудочковых тахиаритмий и внезапной сердечной смерти у пациентов хронической сердечной недостаточностью. Кардиология. 2020; 60(4):101–108. DOI: 10.18087/cardio.2020.4. n487.
   Gasparyan A.Zh., Shlevkov N.B., Skvortsov A.A. Possibilities of modern biomarkers for assessing the risk of developing ventricular tachyarrhythmias and sudden cardiac death in patients with chronic heart failure. Kardiologiia. 2020;60(4):101–108. DOI:10.18087/cardio.2020.4. n487 [in Russian].
6. Алиева А.М., Байкова И.Е., Кисляков В.А. и др. Галектин-3: диагностическая и прогностическая ценность определения у пациентов с хронической сердечной недостаточностью. Терапевтический архив. 2019; 91(9):145–149. DOI: 10.26442/00403660.2019.09.000226.
   Aliyeva A.M., Baykova I.E., Kislyakov V.A. et al. Galactin-3: diagnostic and prognostic value in patients with chronic heart failure. Therapeutic Archive. 2019; 91(9):145–149. DOI: 10.26442/00403660.2019.09.000226. [in Russian].
7. Алиева А.М., Пинчук Т.В., Алмазова И.И. и др. Клиническое значение определения биомаркера крови ST2 у пациентов с хронической сердечной недостаточностью. Consilium Medicum. 2021; 23(6):522–526. DOI: 10.26442/20751753.2021.6.200606.
   Alieva A.M., Pinchuk T.V., Almazova I.I. et al. Clinical value of blood biomarker ST2 in patients with chronic heart failure. Consilium Medicum. 2021; 23(6):522–526. DOI: 10.26442/20751753.2021.6.200606. [in Russian].
8. Алиева А.М., Алмазова И.И., Пинчук Т.В. и др. Фракталкин и сердечно-сосудистые заболевания. Consilium Medicum. 2020; 22(5):83–86. DOI: 10.26442/20751753.2020.5.200186.
   Alieva A.M., Almazova I.I., Pinchuk T.V. et al. Fractalkin and cardiovascular disease. Consilium Medicum. 2020; 22(5):83–86. DOI: 10.26442/20751753.2020.5.200186. [in Russian].
9. Chow S.L., Maisel A.S., Anand I. et al. Role of Biomarkers for the Prevention, Assessment, and Management of Heart Failure: A Scientific Statement from the American Heart Association. Circulation. 2017; 135(22): e1054–91. DOI: 10.1161/ CIR.0000000000000490.
10. Dinarello C.A. Biologic basis for interleukin-1 in disease. Blood. 1996; 87(6):2095-147.
11. Szekely Y., Arbel Y. A Review of Interleukin-1 in Heart Disease: Where Do We Stand Today? Cardiol Ther. 2018; 7(1):25-44. DOI: 10.1007/s40119-018-0104-3.
12. Dinarello C.A. Overview of the IL-1 family in innate inflammation and acquired immunity. Immunol Rev. 2018; 281:8–27. DOI: 10.1111/imr.12621.
13. Dinarello C.A. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood. 2011; 117(14):3720-32. DOI: 10.1182/blood-2010-07-273417.
14. Buckley L.F., Abbate A. Interleukin-1 blockade in cardiovascular diseases: a clinical update. Eur Heart J. 2018; 39(22):2063-2069. DOI:10.1093/eurheartj/ehy128.
15. Dinarello C.A. The IL-1 family of cytokines and receptors in rheumatic diseases. Nat Rev Rheumatol. 2019; 15:612–632. DOI:10.1038/s41584-019-0277-8.
16. Abbate A., Toldo S., Marchetti C. et al. Interleukin-1 and the Inflammasome as Therapeutic Targets in Cardiovascular Disease. Circ Res. 2020; 126(9):1260-1280. DOI: 10.1161/CIRCRESAHA.120.315937.
17. Weber A., Wasiliew P., Kracht M. Interleukin-1 (IL-1) pathway. Sci Signal. 2010; 3(105):cm1. DOI: 10.1126/scisignal.3105cm1.
18. Cremer P.C., Kumar A., Kontzias A. et al. Complicated Pericarditis: Understanding Risk Factors and Pathophysiology to Inform Imaging and Treatment. J Am Coll Cardiol. 2016; 68(21):2311-2328. DOI: 10.1016/j.jacc.2016.07.785.
19. Braunwald E. Biomarkers in heart failure. N Engl J Med. 2008; 358(20):2148-59. DOI:10.1056/NEJMra0800239.
20. Liu S.J., Zhou W., Kennedy R.H. Suppression of beta-adrenergic responsiveness of L-type Ca2+ current by IL-1beta in rat ventricular myocytes. Am J Physiol. 1999; 276(1):H141-8. DOI: 10.1152/ajpheart.1999.276.1.H141.
21. Combes A., Frye C.S., Lemster B.H. et al. Chronic exposure to interleukin 1beta induces a delayed and reversible alteration in excitation-contraction coupling of cultured cardiomyocytes. Pflugers Arch. 2002; 445(2):246-56. DOI:10.1007/s00424-002-0921-y.
22. Tatsumi T., Matoba S., Kawahara A. et al. Cytokine-induced nitric oxide production inhibits mitochondrial energy production and impairs contractile function in rat cardiac myocytes. J Am Coll Cardiol. 2000; 35(5):1338-46. DOI: 10.1016/s0735-1097(00)00526-x
23. Nadar S.K., Shaikh M.M. Biomarkers in Routine Heart Failure Clinical Care. Card Fail Rev. 2019; 5(1):50-6. DOI:10.15420/cfr.2018.27.2
24. Anand I.S., Rector T.S., Kuskowski M. et al. Prognostic value of soluble ST2 in the Valsartan Heart Failure Trial. Circ Heart Fail. 2014; 7(3):418-26. DOI:10.1161/CIRCHEARTFAILURE.113.001036.
25. Felker G.M., Fiuzat M., Thompson V. et al. Soluble ST2 in ambulatory patients with heart failure: Association with functional capacity and long-term outcomes. Circ Heart Fail. 2013; 6(6):1172-9. DOI: 10.1161/CIRCHEARTFAILURE.113.000207.
26. Daniels L.B., Bayes-Genis A. Using ST2 in cardiovascular patients: a review. Future Cardiol. 2014; 10(4):525-39. DOI:10.2217/fca.14.36.
27. Van Tassell B.W., Seropian I.M., Toldo S., et al. Interleukin-1β induces a reversible cardiomyopathy in the mouse. Inflamm Res. 2013; (7):637-40. DOI: 10.1007/s00011-013-0625-0.
28. Van Tassell B.W., Arena R.A., Toldo S. et al. Enhanced interleukin-1 activity contributes to exercise intolerance in patients with systolic heart failure. PLoS One. 2012; 7(3): e33438. DOI: 10.1371/journal.pone.0033438.

29. Zhu J., Zhang J., Xiang D., et al. Recombinant human interleukin-1 receptor antagonist protects mice against acute doxorubicin-induced cardiotoxicity. Eur J Pharmacol. 2010; 643(2-3):247-53. DOI: 10.1016/j.ejphar.2010.06.024.
30. Mezzaroma E., Mikkelsen R.B., Toldo S., et al. Role of Interleukin-1 in Radiation-Induced Cardiomyopathy. Mol Med. 2015; 21(1):210-8. DOI:10.2119/molmed.2014.00243.
31. Ikonomidis I., Lekakis J.P., Nikolaou M. et al. Inhibition of interleukin-1 by anakinra improves vascular and left ventricular function in patients with rheumatoid arthritis. Circulation. 2008; 117(20):2662-9. DOI: 10.1161/CIRCULATIONAHA.107.731877.
32. Abbate A., Canada J.M., Van Tassell B.W. et al. Interleukin-1 blockade in rheumatoid arthritis and heart failure: a missed opportunity? Int J Cardiol. 2014; 171(3): e125–e126. DOI: 10.1016/j.ijcard.2013.12.078.
33. Van Tassell B.W., Arena R., Biondi-Zoccai G. et al. Effects of interleukin-1 blockade with anakinra on aerobic exercise capacity in patients with heart failure and preserved ejection fraction (from the D-HART pilot study). Am J Cardiol. 2014; 113(2):321-327. DOI: 10.1016/j.amjcard.2013.08.047.
34. Van Tassell B.W., Abouzaki N.A., Oddi Erdle C. et al. Interleukin-1 blockade in acute decompensated heart failure: a randomized, double-blinded, Placebo-Controlled Pilot Study. J Cardiovasc Pharmacol. 2016; 67(6):544–551. DOI: 10.1097/FJC.0000000000000378.
35. Imen T., Salma M., Khouloud C., et al. IL-1β gene polymorphism and serum levels in a Tunisian population with acute heart failure. Biomark Med. 2017; 11(12):1069-1076. DOI:10.2217/bmm-2017-0179.
36. Aleksova A., Beltrami A.P., Carriere C. et al. Interleukin-1β levels predict long-term mortality and need for heart transplantation in ambulatory patients affected by idiopathic dilated cardiomyopathy. Oncotarget. 2017; 8(15):25131-25140. DOI:10.18632/oncotarget.15349.
37. Van Tassell B.W., Canada J., Carbone S. et al. Interleukin-1 Blockade in Recently Decompensated Systolic Heart Failure: Results from REDHART (Recently Decompensated Heart Failure Anakinra Response Trial). Circ Heart Fail. 2017; 10(11): e004373. 117.004373. DOI: 10.1161/CIRCHEARTFAILURE.
38. Butts B., Butler J., Dunbar S.B. et al. ASC Methylation and Interleukin-1β Are Associated with Aerobic Capacity in Heart Failure. Med Sci Sports Exerc. 2017; 49(6):1072-1078. DOI: 10.1249/MSS.0000000000001200.
39. Pascual-Figal D.A., Bayes-Genis A., Asensio-Lopez M.C., et al. The Interleukin-1 Axis and Risk of Death in Patients with Acutely Decompensated Heart Failure. J Am Coll Cardiol. 2019; 73(9):1016-1025. DOI: 10.1016/j.jacc.2018.11.054.
40. Javan H., Li L., Schaaf C.L. et al. Interleukin 1 receptor antagonism abrogates acute pressure-overload induced murine heart failure. Ann Thorac Surg. 2021: S0003-4975(21)01434-X. Epub ahead of print. DOI: 10.1016/j.athoracsur.2021.07.044.
41. Abbate A., Wohlford G.F., Del Buono M.G. et al. Interleukin-1 blockade with Anakinra and heart failure following ST-segment elevation myocardial infarction: results from a pooled analysis of the VCUART clinical trials. Eur Heart J Cardiovasc Pharmacother. 2021 Oct 7: pvab075. Epub ahead of print. DOI: 10.1093/ehjcvp/pvab075.
42. Van Tassell B.W., Buckley L.F., Carbone S. et al. Interleukin-1 blockade in heart failure with preserved ejection fraction: rationale and design of the Diastolic Heart Failure Anakinra Response Trial 2 (D-HART2). Clin Cardiol. 2017; 40(9):626-632. DOI: 10.1002/clc.22719.