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Dynamics of immuno-inflammatory markers in patients with chronic heart failure after myocardial infarction during treatment with rosuvastatin

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Abstract: In the occurrence and progression of chronic heart failure (CHF), the role of pro- inflammatory cytokines has been established: tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which induce the synthesis of C-reactive protein (CRP), an increasing the level of these markers leads to the progression of CHF. It was determined that with the development of the maladaptive phase of left ventricular remodeling, there is a sharp rise in the level of pro- inflammatory cytokines and serum CRP, which are closely interrelated with the structural and functional changes of the left ventricle in CHF. Against the background of taking rosuvastatin at a daily dose of 20 mg, there is a decrease in the levels of pro-inflammatory cytokines and serum CRP and a positive dynamics of heart remodeling indicators.

Keywords: Systemic inflammation, left ventricular remodeling, rosuvastatin, chronic heart failure.

Introduction: In addition to the cardiac, hemodynamic and neurohumoral concepts of progressive chronic heart failure (CHF) has been developed the theory of immune activation, according to that, endothelial dysfunction is recognized as one of the main links in the pathogenesis of CHF, induced by oxidative stress and pro- inflammatory cytokines that suppress the production of nitric oxide (NO) [1,3,7]. In the occurrence and progression of CHF, the role of pro-inflammatory cytokines has been established: tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [4,9].

The biological effects of these cytokines

are largely similar: they induce the synthesis of C-reactive protein (CRP), an increasing the level of those, in turn, leads to the progression of CHF [6]. Many authors suggest that pro- inflammatory cytokines play an important role in the progression of CHF, mediating the nature and intensity of myocardial and vascular remodeling processes by regulating the level of apoptosis of cardiomyocytes, which is currently considered as a fundamental mechanism capable of causing irreversible impairment of myocardial contractile activity in CHF [5].

The aim of the study was to study the clinical and laboratory significance of immuno- inflammatory markers (CRP, IL-6 and TNF-α) in patients with CHF during the treatment with rosuvastatin.

METHODS

96 patients with CHF stages I–IIB and functional class I–IV were examined in the cardiology department of the

Bukhara Regional Center of the Republican Scientific Center for Medical Emergencies in Bukhara. There were: 85 men and 11 women, aged 40 to

80 years (mean age 60.73 ± 9.86 years). Previously, all patients had suffered a myocardial infarction (MI) of various statutes of limitations - from 1 to 21 years (average 10.61

± 7.26 years). Criteria for inclusion in the study: the presence in patients of CHF of ischemic etiology. To objectify FC CHF, a test with a 6- minute walk in a 35-meter long corridor marked every 5 meters was carried out and the clinical condition of patients was assessed according to the modified V.Yu. Mareev in 2000 on the clinical assessment scale (SHOKS) in CHF. Drug treatment included angiotensin- converting enzyme inhibitors, β-blockers, diuretics, if necessary, nitrates, cardiac glycosides. At the time of inclusion in the study, patients did not take lipid-lowering drugs or stopped taking them for various reasons at least 6 weeks before the study. All patients were prescribed rosuvastatin (Mertenil, Gedeon Richter company) at a daily dose of 20 mg once. The duration of therapy was 12 weeks, after that all patients were re-examined. All of them underwent a general clinical examination, which included the collection of anamnesis and assessment of objective data; complex ultrasound examination of the heart.

The following indicators were determined:

final systolic and diastolic dimensions (FDD, FSD, cm) and volumes (FDV, FSV, ml) of the left ventricle (LV); ejection fraction (EF, %); the thickness of the interventricular septum in systole and diastole (IVSd, IVSs, mm); thickness of the posterior wall in systole and diastole (ThPWs, ThPWd, mm); the myocardial mass of LV (MM, g); stroke volume (SV, ml); minute volume (MV, ml/min). The relative thickness of wall (RTW) of the LV was calculated using the formula: RTW = (IVSd + ThPWd)/FDD. Systolic myocardial stress (MS in dynes/cm2) was calculated using the formula: MS = BPs × FSD/4 × ThPWs × (1 + ThPW/FSD), where BPs is

systolic blood pressure. To assess myocardial contractile activity, the EF/MS index proposed by K. Taniguchi and co-authors was used. (2000) , which reflects the degree of adequacy of the global systolic function of the heart to the test load with a given LV geometry [10].Diastolic properties of LV were studied using the study of transmitral diastolic flow (TMDF) by determining the maximum TMDF velocity during early LV filling (Ve, m/s), the maximum TMDF velocity during late LV filling (Va, m/s), the ratio of maximum velocities flows in the period of early and late filling (E/A), time of isovolumic relaxation of the left ventricle (TIR, ms). The content of CRP (Vector-Best, Russia) and pro-inflammatory cytokines: TNF- α and IL-6 (Protein contour, St. Petersburg) were determined in the blood serum of patients by enzyme immunoassay using appropriate test systems. When examining a group of healthy people, the average levels of IL-6 (7.27

± 0.42 pg/ml) and TNF-α (4.62 ± 0.19 pg/ml) were determined. Data analysis was carried out using parametric and nonparametric statistical methods. After a preliminary analysis of the distribution of the studied features for normality, the mean value (M) and standard error (m) were calculated. The significance of the differences between the compared parameters was calculated using the method of variation statistics according to Student's t-test. The difference between the compared indicators was taken as reliability $p < 0.05$. To identify correlations between the

differences and the parameters, a calculation was carried out using the Pearson squares method. The correlation between the estimated parameters was considered reliability at $p < 0.05$.

RESULTS AND DISCUSSION

All patients were divided into 2 groups depending on the severity of left ventricular remodeling according to echocardiography, according to OSSN criteria (2010). Group 1 included 67 (69%) patients with adaptive LV remodeling (stages I–IIA), group 2 included 29 (31%) patients with incompatible LV remodeling (stage IIB). During the observation period, 6 (6.25%) adverse cardiovascular events occurred. 2 patients of group 1 and 4 patients of group 2 died. The cause of death of one patient from group 1 was complex arrhythmias, the other - complications of myocardial infarction. In group 2, the cause of death was progressive heart failure. From the presented data, it can be seen that patients with maladaptive remodeling had significantly more severe manifestations of CHF: a higher FC of circulatory failure and a more significant decrease in exercise tolerance. It was also noted that the development of CHF is accompanied by a change primarily in the geometry of the LV and an increase in the mass of the LV myocardium. As CHF progressed, an increase in the linear dimensions of the LV cavity was observed. In patients with the development of maladaptive remodeling, there was a decrease in the relative LV wall thickness index, which indicates the development of eccentric hypertrophy of LV and the progression of maladaptive remodeling LV , the severity of which increases with the increase in CHF FC. In patients with adaptive LV remodeling, concentric hypertrophy of LV prevailed (77%), and in 23% of cases in this group of patients, the development of eccentric hypertrophy of LV was noted. In the study of diastolic function, it was found that the 1st type of diastolic dysfunction

prevailed in patients with adaptive LV remodeling, and the 2nd type prevailed in patients with maladaptive LV remodeling. Changes in the levels of the studied cytokines in the blood serum and the concentration of CRP in patients with CHF were characterized by their significant increase with the progression of CHF (Table 1).

The maximum level of cytokines (TNF-α

and IL-6) was found in patients with maladaptive left ventricular remodeling. In patients with adaptive LV remodeling, there was also an increase in the level of TNF-α in blood serum, but it was insignificant compared to the group of healthy individuals. There was no significant difference in the level of IL-6 with the group of healthy subjects. The level of CRP in the blood serum before treatment was increased both in group 1 and in group 2, and amounted to 25.99 ± 16.3 and 43.41 ± 11.19 mg/l, respectively, which is significantly higher than normal values.

Table 1.

Dynamics of inflammation markers and laboratory parameters before and after treatment with rosuvastatin

Indicators	Group 1 (n =67)		Group 2 (n=29)	
	Before treatment	After 3 months	Before treatment	After 3 months
CRP, mg/l	25,99±16,3	9,66±6,54	43,41±11,19	15,32±9,6
IL-6, pg/ml	4,43±2,32	2,32±1,83	27,76±15,33	7,36±1,85
TNF-α, pg/ml	11,1±7,62	3,4±0,9	39,1±24,5	10,3±7,65
Cholesterol, mmol/l	5,52±1,4	4,19±0,46	3,9±0,86	3,64±0,7
LDL, mmol/l	3,66±0,91	2,64±0,64	2,69±0,6	2,34±0,7
TAG, mmol/l	2,0±1,3	1,27±0,75	1,43±0,32	1,13±0,25

Note LDL - low density lipoproteins; TAG, triacyglycerides;

Significant difference ($p < 0.05$) from pre- treatment scores; ** Significant difference ($p < 0.05$) from the same indicator in group 1.

We have established a relationship bet- ween the levels of pro-inflammatory cytokines in the blood serum and the morpho-functional parameters of the left ventricle. In the group of patients with maladaptive remodeling, a correlation between TNF-α and myocardial mass was noted ($r = 0.65$; $p < 0.05$); MS ($r = 0.63$; $p < 0.05$); with the state of diastolic function: peak E and E/A ($r = 0.72$; $p < 0.05$, $r = 0.58$; $p < 0.05$).

There was no connection with EF, but there was a correlation with the EF/MS index, which characterizes the specific contractility of the myocardium ($r = 0.46$; $p < 0.05$). In patients with adaptive LV remodeling, IL-6 correlated with MS ($r = 0.39$; $p < 0.05$) and LV wall thickness ($r = 0.75$; $p < 0.05$), while TNF-α correlated with LDL ($r = 0.41$; $p < 0.05$) and TAG ($r = 0.38$; $p < 0.05$). Thereafter, the results of this study demonstrated that the levels of pro- inflammatory cytokines in the serum of patients with CHF are associated with the development and severity of clinical manifestations of CHF. A previously undescribed abrupt increase in serum pro- inflammatory cytokines was found in patients with maladaptive LV remodeling.

Against the background of taking rosuvastatin at a daily dose of 20 mg, a positive trend in the clinical manifestations of CHF was noted, which was characterized by a significant decrease in the FC of CHF and an increase in exercise tolerance according to the test with a 6-minute walk in both group 1 and group 2. There was a significant decrease in myocardial mass, and a decrease in FDV and FSV. An improvement in myocardial contractility was noted, and the EF/MS index increased by 14.2 and 36.0% in patients with adaptive and maladaptive remodeling, respectively. A positive change in the structural and functional state of the left ventricle was accompanied by an improvement in the diastolic function of the left ventricle in the form of a positive change in the structure of diastolic filling (E/A) in both groups.

After 12 weeks of the study, in patients with both adaptive and maladaptive LV remodeling, against the background of clinical improvement, a significant decrease in the concentration of CRP and pro-inflammatory cytokines (IL-6, TNF-α) in the blood serum was noted. All patients at the time of inclusion in the study according to the SCORE scale for assessing the risk of death from cardiovascular diseases were in the high and very high-risk group. In 62% of patients, after 3 months from the start of treatment with rosuvastatin at a daily dose of 20 mg, the target LDL level (< 2.5 mmol / l) was achieved.

Our data are largely consistent with the literature data on the adverse effect of pro- inflammatory cytokines on the initiation, becoming and progression of LV ischemic dysfunction [8]. They also indicate a close relationship

between the processes of LV remodeling in CHF and the mechanisms of the immune response, which is activated in this disease. The detected significant abrupt increase in the levels of pro-inflammatory cytokines and CRP during the development of the maladaptive phase of heart remodeling can serve as a criterion for the severity of CHF and become the starting point in the clinician's reasoning about the intensity (aggressiveness) of the therapeutic effect. The results of our study showed that rosuvastatin therapy is not only accompanied by a hypolipidemic effect, but also leads to a significant decrease in the concentration of pro-inflammatory cytokines in the blood serum and CRP in patients with CHF of ischemic etiology. In our study, the level of CRP significantly decreased during treatment with rosuvastatin in both groups, which indicates a decrease in inflammation and is associated with a decrease in cardiac decompensation and, accordingly, the risk of an unfavorable course.

This is consistent with the results of a number of studies, which also noted a correlation between the level of pro- inflammatory cytokines and the severity of clinical manifestations of CHF, a decrease in life expectancy, and a decrease in their concentration during treatment is associated with clinical improvement [2].

Thus, after 12 weeks, most patients reach- ed the target level of blood lipids, but even more important to us is the pronounced effect of this treatment on the level of pro-inflammatory cytokines and CRP, which may contribute to the inhibition of the development of the disease.

CONCLUSION

1. The development of the maladaptive phase of LV remodeling is accompanied by a sharp rising the level of pro-inflammatory cytokines and CRP in the blood serum.

2. There is a significant correlation of pro-inflammatory cytokines with structural and functional changes in the heart in CHF.

3. Treatment with rosuvastatin (Mertenil drug) at a dose of 20 mg in patients with CHF of ischemic etiology is accompanied by a decrease in the level of pro-inflammatory cytokines (TNF-α, IL-6), serum CRP and an improvement in the structural and functional state of the LV in patients with CHF of ischemic etiology.

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