AN OBSERVE AND CORRECTION OF THE HAEMODYNAMICAL DISORDERS OF SYSTEMIC SCLEROSIS

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Abstract

The purpose *of the study is observing of the damage of the cardiovascular system in patients with systemic scleroderma (SS).* ***Materials and methods.*** *Clinical research was conducted in 90 patients with a diffuse form of SS, aged 25 to 58 years (average age 39,1±5 years), with an average disease duration of 8.2±6 years, were involved in the study. All patients involved in the study were divided into three groups according to the type of treatment: patients in 1st group (n-42) received conventional treatment according to the recommendations of the standard of care for SS, 2nd group (n-48) received treatment according to the standard of care for patients in the 2nd group(n-38) statin (atorvastatin drug in the amount of 20-40 mg for 6 months) in addition to traditional treatment, tocilizumab (8 mg/kg) according to the scheme (8 mg/kg) dose in the form of injection once every 4 weeks) was prescribed for 6 months.* ***Results****. According to the obtained results, when the changes in the systolic and diastolic volume of the left ventricle during the study were studied, the changes in the systolic volume of the left ventricle reliably increased in patients of 1st group compared to the beginning of the study, while in 2nd group, this indicator did not change, which is confirmed by the unreliable change of values in statistical analysis. Also, in the 3rd group, it was seen that the heart remodeling was shifted in a positive direction with a reliable decrease in end-systolic volume of left ventricular (ESVLV). Left ventricular fraction (LVF), which is the main gradient determining the functional state of the left ventricle, showed negative results in the 1st group of patients, decreasing in reliable values during our study. In the 2nd group of patients who received atorvastatin in addition to conventional treatment, this indicator changed unreliable, that is, the values shifted in one direction or another. The thickness of carotid arteries (TCA), which is considered a vascular component of cardiovascular system changes, changed as follows during six months of treatment in our research: in 1st group, the thickness of IMC showed a worsening of the process even though it was at less reliable ($p<0.05$) values. In 2nd group, the values did not change. In patients of 3rd group who received atorvastatin and tocilizumab drugs in addition to traditional treatment, the IMC thickness decreased reliably ($p<0.01$) after treatment and reflected positive results.* ***Conclusion****. In patients with SS, negative changes were detected in the cardiovascular system according to the results of ECG and EchoCG examination, in particular, left ventricular hypertrophy - in 46% of*

cases, coronary insufficiency - in 35%, and the end systolic volume of the left ventricle was found in 51% and increased myocardial mass by 68%. In patients with systemic scleroderma, pathological enlargement of the intima-media complex of the common carotid artery (>0.9 mm) was detected in 35% of cases, atherosclerotic plaques in 21% of patients.

Keywords: *systemic sclerosis, cardiovascular system, IL-6, treatment, statins, gene engineering drugs*

Systemic sclerosis (SS) is a chronic autoimmune disease belonging to the group of systemic connective tissue diseases characterized by progressive generalized damage to the skin, musculoskeletal system, internal organs, and blood vessels [1-3]. It is considered a rare disease and is an autoimmune pathology with a poor prognosis. Primary incidence of SS ranges from 3.7 to 19 cases per million population per year [5,8]. Mortality rate is 1.4 to 5.3 per million population per year. In the following decades, the prevalence of SS increased from 4 to 126 cases per 1 million population [6]. This is due to the improvement of diagnosis in the field and the real increase of the disease. The maximum incidence occurs on average at the age of 30-50 years. Usually, SS affects more women than men (in a ratio of 5-7:1). 10% of the disease occurs in childhood [4,14]. In addition, generalized injury of blood vessels is a characteristic feature of SS, and the pathogenesis of this disease lies in the predisposition to the development of atherosclerosis [7,11]. It is currently confirmed that more than 50-60% of SS patients have atherosclerotic damage in medium and large-caliber blood vessels [9-10]. Vascular occlusion and wall inflammation lead to tissue damage in SS [12]. IL-6 plays a special role in these processes, it disrupts the ratio of atherogenic and antiatherogenic lipids, lipoproteins and their protein components [15]. The negative effect of increased IL-6 on the development of atherosclerosis has been proven in many studies [13].

The purpose of the study is observe damage of the cardiovascular system in patients with systemic scleroderma and evaluate ways of its correction.

Materials and methods of research: clinical research was conducted in 2020-2022 in the multidisciplinary clinic of rheumatology and arthrology, cardiorheumatology and arthrological specialized outpatient treatment course of the Tashkent Medical Academy. 90 patients with a diffuse form of SS, aged 25 to 58 years (average age 39,1±5 years), with an average disease duration of 8,2±6 years, were involved in the study. 75 (85%) of them were women and 15 (15%) were men. The diagnosis of SS is based on the classification criteria presented in modern clinical guidelines, as well as the 2013 European Antirheumatic League (EULAR) and the 2016 American College of Rheumatology (ACR) international criteria. As a control group, 30 healthy individuals, matched to patients with SS in terms of gender, age, risk factors, arterial blood pressure, lipid spectrum, were taken.

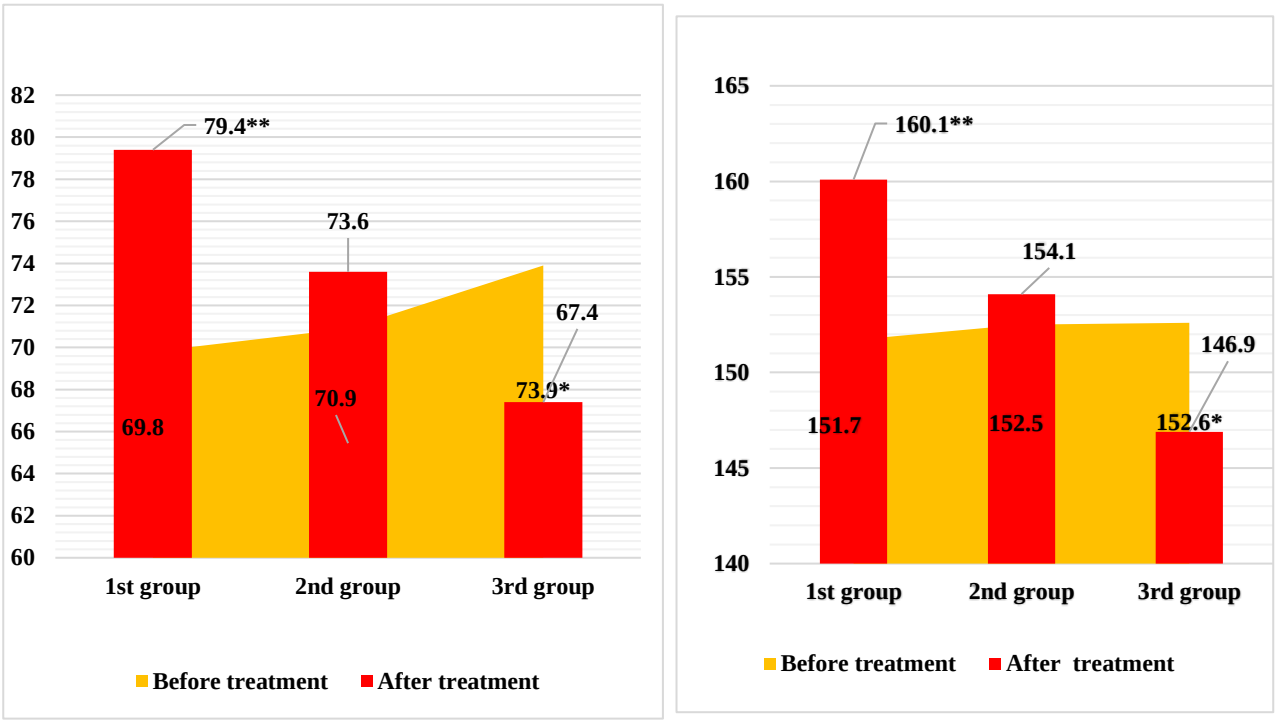
All patients involved in the study were divided into three groups according to the type of treatment: patients in 1st group (n-42) received conventional treatment according to the recommendations of the standard of care for SS, 2nd group (n-48) received treatment according to the standard of care for patients in the 2nd group (n-38) statin (atorvastatin drug in the amount of 20-40 mg for 6 months) in addition to traditional treatment, tocilizumab (8 mg/kg) according to the scheme (8 mg/kg) dose in the form of injection once every 4 weeks) was prescribed for 6 months.

Before treatment and after treatment, general clinical (general blood analysis, general urine analysis), biochemical (AlT, AsT, bilirubin, urea, creatinine, total protein), lipid spectrum indicators (Chol, LDLP, HDLP, TG), cytokine (IL-6) was checked in blood serum based on immunological examinations (SRP, RF) and special laboratory analyses. Also, ECG, EchoCG,

chest x-ray, USD of internal organs, EGDFS according to the instructions, dopplerography of the carotid artery were conducted. Blood lipid spectrum indicators were determined by HUMAN (Germany) equipment Chol, LDLP, HDLP, TG. Doppler imaging of both carotid arteries was performed on Samsung Medison SonoAce X6 (CHINA) to detect signs of early atherosclerosis. An increase in the thickness of the intima media complex (IMC) (from 0.9 to 1.2 mm) and an atherosclerotic plaque (local enlargement of the IMC ≥ 1.2 mm) were used as criteria for atherosclerotic damage to the vessels. Through this examination, the thickness of IMC of the right and left carotid arteries was checked and their average was calculated. In this way, atherosclerotic damage of vessels was evaluated.

Result. According to the results, when the changes in the left ventricular end-systolic and diastolic volume were studied during the study, the changes in the left ventricular end-systolic volume reliably increased in patients of 1st group compared to the beginning of the study, while in 2nd group , this indicator did not change, which was confirmed by the unreliable change of values in statistical analysis. Also, in the 3rd group, it was seen that the heart remodeling was shifted in a positive direction with a reliable decrease in ESVLV. Analysis of left ventricular end-diastolic volume showed a significant increase in EFLV in patients of 1st group compared to the beginning of the study. This is a sign of a negative shift in cardiac remodeling. In the 2nd group, it was observed that this indicator did not change. Also, in the 3rd group consisting of patients who received statin and tocilizumab in addition to traditional treatment for 6 months, it was

observed that a positive result was recorded with a reliable reduction of EDVLV (Fig. 1).



Note: * - differences are significant compared to pre-treatment values (*- p<0.05)

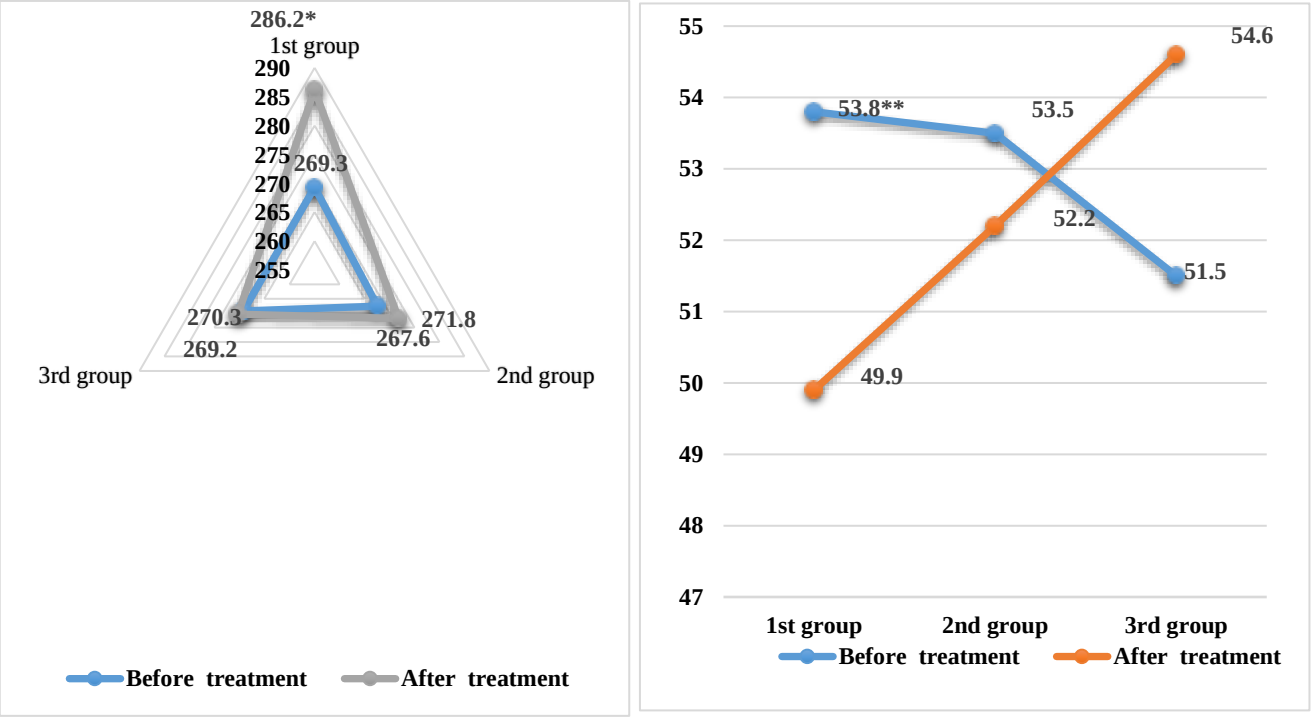
**** - differences are significant compared to pre-treatment values (**- p<0.01)**

Figure 1. Left ventricular end systolic and diastolic volume changes during the study

The mass of left ventricular myocardium, which is a measure of heart volume index, reliably increased in patients of 1st group compared to the beginning of the study, indicating that left ventricular hypertrophy continues rapidly, while in 2nd group, this indicator changed in unreliable values. In 3rd group, which received an additional statin and tocilizumab drug to the conventional treatment, MMLV showed a significant slowing

down of the left ventricular hypertrophy process, with unreliable changes in accordance with the values at the end of the study. Left ventricular fraction, which is the main gradient determining the functional state of the left ventricle, showed negative results in the 1st group of patients, decreasing in reliable values during our study. In the 2nd group of patients who received atorvastatin in addition to conventional treatment, this

indicator changed unreliable, that is, the values shifted in one direction or another. And in the 3rd group, consisting of patients who received additional statin and tocilizumab drug to conventional treatment during 6 months, a reliable increase of EFLV from 51.5% to 54.6% is a positive result in heart function (Figure 2).



Note: * - differences are significant compared to pre-treatment values (*- p<0.01) ** - differences are significant compared to pre-treatment values (- p<0.05).**

Figure 2. Changes in left ventricular myocardial mass and ejection fraction during the study

The formation of vascular pathology in patients with SS is manifested by the detection of atherosclerotic plaques and thickening of the IMC in the carotid arteries.

Therefore, in our research, when we analyzed the results of the changes in the thickness of the carotid arteries in research groups consisting of SS patients of different ages, in the group of SS patients aged 18-30 years, the thickness of the IMC was 0.92±0.05 mm, which was less reliable than the control group (p< 0.05) was found to change. In the group of 31-40-year-old

patients with SS, the thickness of IMC was 0.99±0.06 mm and it was observed that it changed reliably ($p<0.01$) compared to the control group. In the group of 41-50-year-old patients with SS, the thickness of IMC was determined to be 1.08±0.06 mm, and the result was confirmed by statistical analysis as a reliable ($p<0.01$) thickening compared to the control group.

This part of our scientific research shows that in patients with SS, one of the main risk factors of early atherosclerosis, IMC begins to thicken compared to the norm, even in patients of the age group. This is explained by the fact that when we divided our patients with SS into three groups according to age, the results of IMC values were thickened with a certain reliability in all groups (Table 1).

Table 1

Comparative analysis of indicators of the common carotid artery

Indicators	Control group (n-30)	Patients with SS n-90		
		18-30 years n-25	31-40 years n-38	41-50 years n-27
Intima media complex of carotid arteria (mm)	0,77±0,03	0,87±0,05*	0,99±0,06**	1,08±0,06**

Note: * - differences are significant compared to the indicators of the control group (*- p<0.05, ** - p<0.01)

intima-media complex in patients and the control group by age

When studying the association of IMC indicators with the frequency of occurrence of risk factors (RF) in patients with SS, it can be seen that even in patients without RF, the IMC indicator exceeded 0.9 mm, and this is 22.2%, and in patients with more than 5 risk factors, this indicator It was found in 63.6% (Fig. 3).

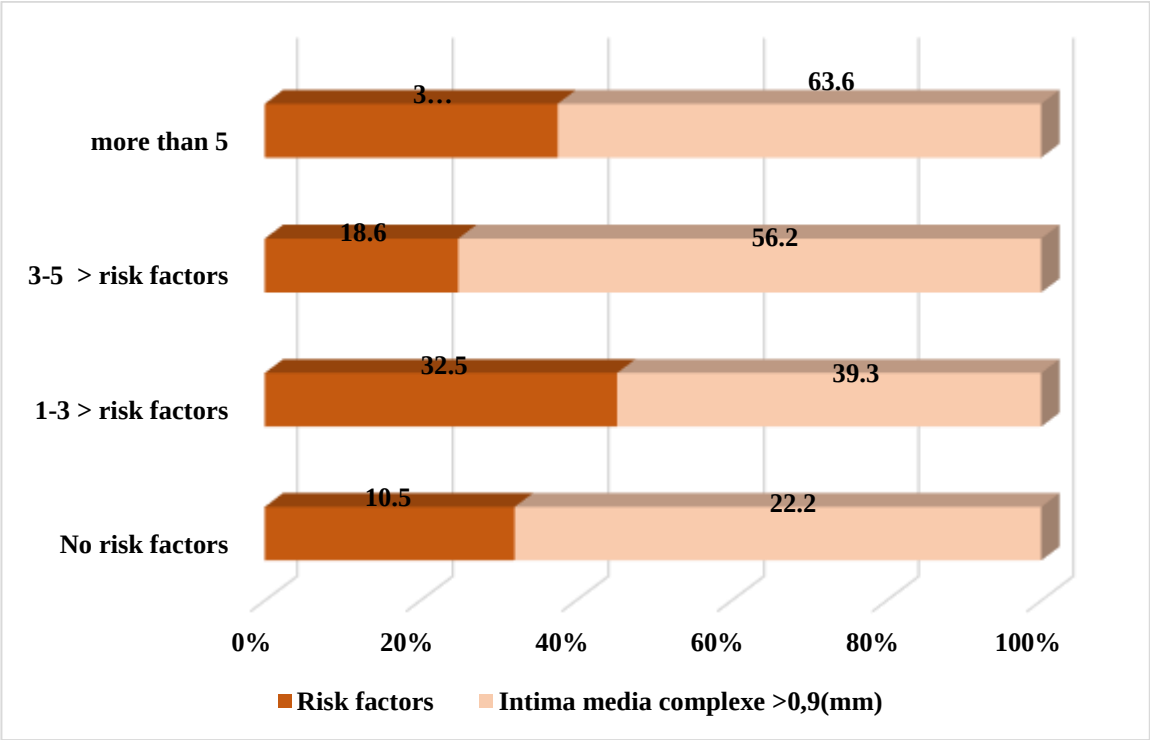
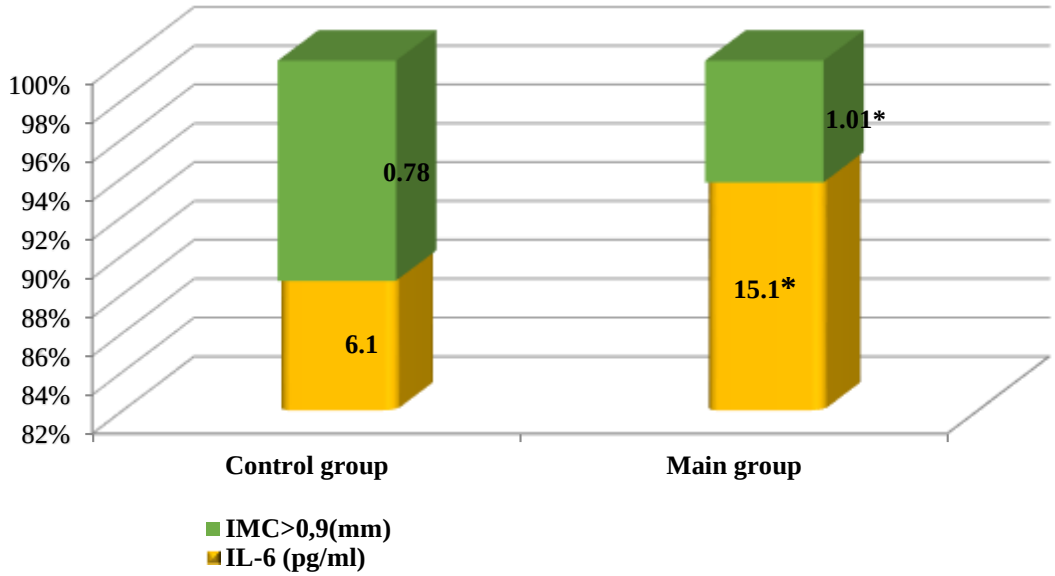


Figure 3. Correlation of indicators of intima-media complex with risk factors in patients with systemic scleroderma

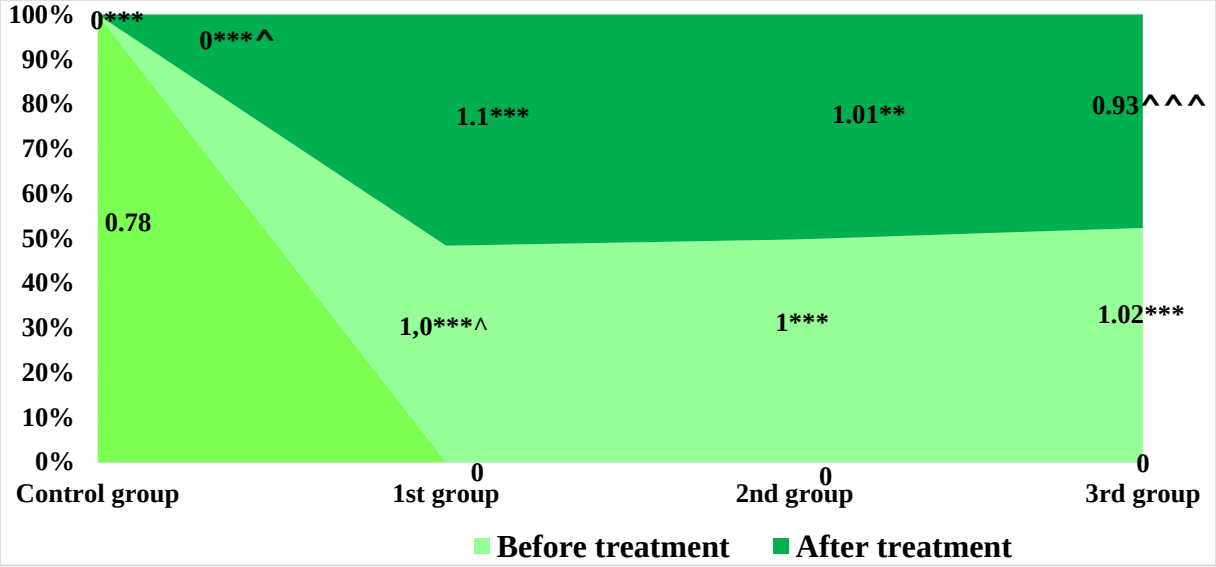
When studying the change of IL-6 in relation to the IMC indicator, compared to the control group, it was observed that the thickness of IMC exceeded 0.9 mm with an increase in the interleukin-6 content in the main group, and this value was 1 mm on average (Fig. 4).



Note: * - differences are significant compared to the indicators of the control group (*- p<0.01)

Figure 4. Changes in the amount of interleukin-6 in relation to the index of the intima-media complex

The thickness of carotid arteries, which is considered a vascular component of cardiovascular system changes, changed as follows during six months of treatment in our research: in 1st group, the thickness of IMC showed a worsening of the process even though it was at less reliable ($p<0.05$) values. In 2nd group, the values did not change. In patients of 3rd group who received atorvastatin and tocilizumab in addition to traditional treatment showed positive results with a reliable ($p<0.01$) decrease in IMC thickness after treatment (Figure 5).



Note: * - differences are significant compared to the indicators of the control group (*- p<0.05, ** - p<0.01, * - p<0.001); ^ - differences are significant compared to pre-treatment indicators (^ - p<0.05, ^^ - p<0.01, ^^^ - p<0.001).**

Figure 5. Changes in the indicator of the carotid artery intima-media complex against the background of treatment

We interpret this situation as a reflection of coordinated dyslipidemia processes in blood vessels due to the blocking of IL-6 cytokine activity by monoclonal antibody drugs.

Thus, the analysis of the state of the cardiovascular system showed us a reliable reduction of EFLV compared to the beginning of the study in patients of 3rd group who were fully treated with atorvastatin and tocilizumab in addition to traditional treatment, a slight increase of EFLV index, i.e. slowing down of cardiac hypertrophy, and most importantly EFLV showed that it increased in reliable values. These changes are considered a positive shift in cardiac remodeling. Also, in this group, the thickness of carotid artery blood vessels decreases reliably after the treatment of IMC, which once again proves the effectiveness of this new recommendation. We interpret these positive results as a picture of coordinated dyslipidemia processes in the cardiovascular system due to the blocking of IL-6 cytokine activity by monoclonal antibody drugs.

Conclusion. In patients with systemic scleroderma, negative changes were detected in the cardiovascular system according to the results of ECG and EchoCG examination, in particular, left ventricular hypertrophy - in 43% of cases, coronary insufficiency - in 30%, and the end systolic volume of the left ventricle was found in 47% and was manifested by an increase in myocardial mass by 66%. In patients with systemic scleroderma, pathological enlargement of the intima-media complex of the common carotid artery (>0.9 mm) was detected in 32.4% of cases, atherosclerotic plaques in 18.6% of patients.

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