

## VIEW ON INDICATORS OF DAMAGE OF CARDIOVASCULAR SYSTEM OF PATIENTS WITH SYSTEMIC SCLERODERMIA

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### Abstract

Despite many years of scientific research, the final concept of the pathogenesis and treatment of systemic scleroderma (SSD) compared to other systemic rheumatic diseases has not been reached. The microcirculatory vasculature is also the main target in SSD. **The purpose** of the study is to evaluate the damage to the cardiovascular system in patients with systemic scleroderma. **Materials and methods.** Clinical research was conducted in 86 patients with a diffuse form of SSD, aged 18 to 50 years (average age  $37.6 \pm 10.3$  years), with an average disease duration of  $10.7 \pm 7.9$  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-34) received conventional treatment according to the recommendations of the standard of care for SSD, 2<sup>nd</sup> group (n-29) received treatment according to the standard of care for patients in the 2<sup>nd</sup> group (n-29) 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 1<sup>st</sup> group compared to the beginning of the study, while in 2<sup>nd</sup> group, this indicator did not change, which is confirmed by the unreliable change of values in statistical analysis. Also, in the 3<sup>rd</sup> 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 2<sup>nd</sup> 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 1<sup>st</sup> group, the thickness of IMC showed a worsening of the process even though it was at less reliable ( $p < 0.05$ ) values. In 2<sup>nd</sup> group, the values did not change. In patients of 3<sup>rd</sup> 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 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 increased 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.

**Keywords:** Systemic Scleroderma, Cardiovascular System, IL-6, Treatment, Statins, Tocilizumab.

### INTRODUCTION

Systemic scleroderma 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 [1-4]. It is considered a rare disease and is an autoimmune pathology with a poor prognosis. Primary incidence of SSD ranges from 3.7 to 19 cases per million population per year [8]. Mortality rate is 1.4 to 5.3 per million

population per year. In the following decades, the prevalence of SSD 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, SSD affects more women than men (in a ratio of 5-7:1). 10% of the disease occurs in childhood [5,14]. In addition, generalized injury of blood vessels is a characteristic feature of SSD, 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 SSD patients have atherosclerotic damage in medium and large-caliber blood vessels [9-10]. Vascular occlusion and wall inflammation lead to tissue damage in SSD [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 to assess the damage to the cardiovascular system in patients with systemic scleroderma.

## MATERIALS AND METHODS OF RESEARCH

Clinical research was conducted in 2021-2023 in the multidisciplinary clinic of rheumatology and arthrology, cardiorheumatology and arthrological specialized outpatient treatment course of the Tashkent Medical Academy. 86 patients with a diffuse form of SSD, aged 18 to 50 years (average age  $37.6 \pm 10.3$  years), with an average disease duration of  $10.7 \pm 7.9$  years, were involved in the study. 75 (87.2%) of them were women and 11 (12.8%) were men. The diagnosis of SSD 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, 26 (86.7%) women and 4 (13.3%) men, matched to patients with SSD in terms of gender, age, risk factors, arterial blood pressure, lipid spectrum, were taken.

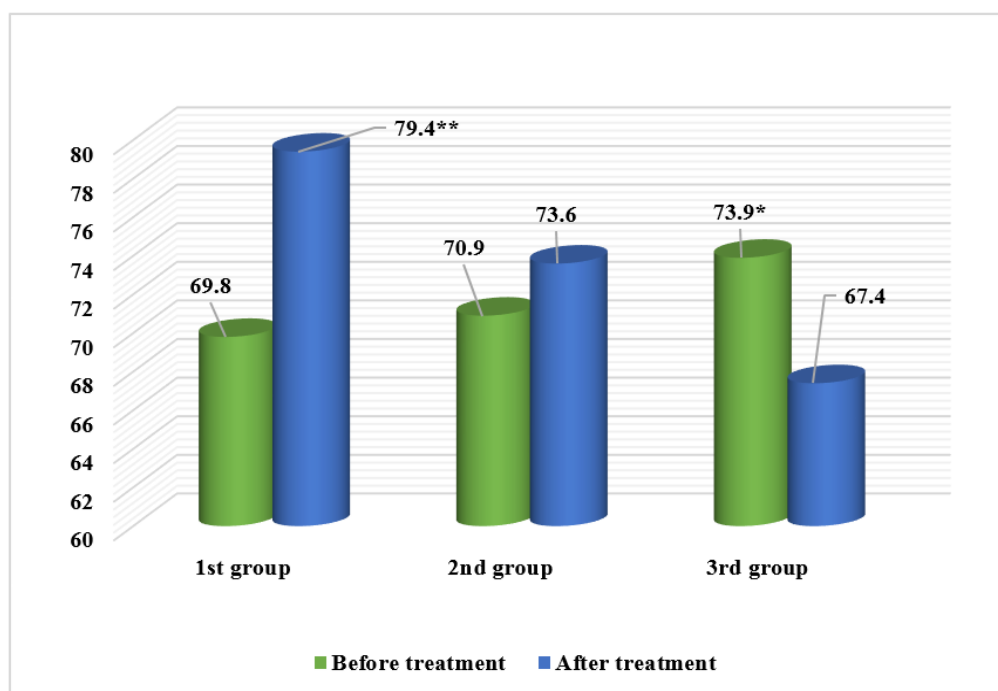
All patients involved in the study were divided into three groups according to the type of treatment: patients in 1<sup>st</sup> group (n-34) received conventional treatment according to the recommendations of the standard of care for SSD, 2<sup>nd</sup> group (n-29) received treatment according to the standard of care for patients in the 2<sup>nd</sup> group (n-29) 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.

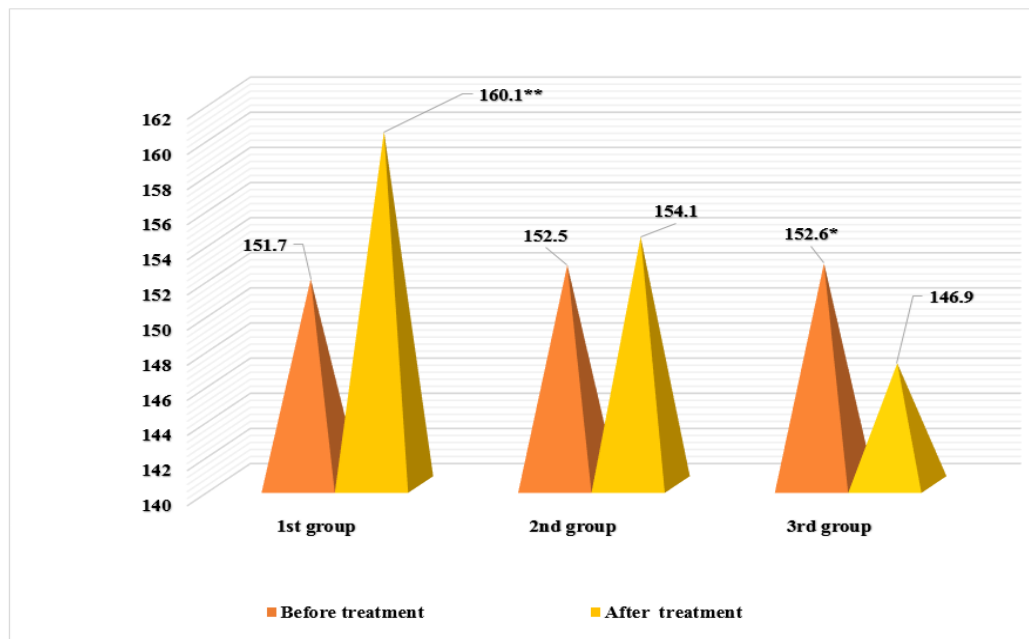
Before treatment and after treatment, general clinical (general blood analysis, general urine analysis), biochemical (AIT, AsT, bilirubin, urea, creatinine, total protein), lipid spectrum indicators (Chol, LDLP, HDLP, TG), cytokine (IL-6) was checked in blood serum based on immunological examinations (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  $\geq 1.2$  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 1<sup>st</sup> group compared to the beginning of the study, while in 2<sup>nd</sup> group, this indicator did not change, which was confirmed by the unreliable change of values in statistical analysis. Also, in the 3<sup>rd</sup> 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 1<sup>st</sup> group compared to the beginning of the study. This is a sign of a negative shift in cardiac remodeling. In the 2<sup>nd</sup> group, it was observed that this indicator did not change. Also, in the 3<sup>rd</sup> 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).



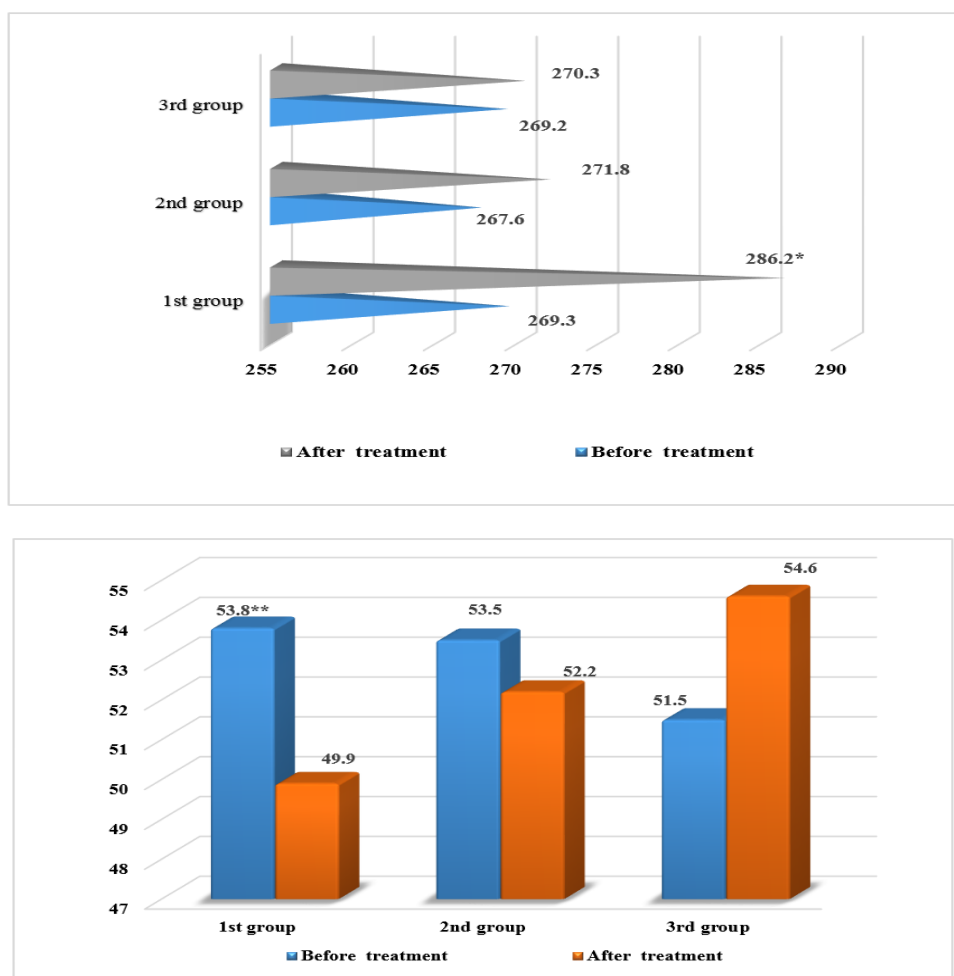


**Figure 1: Left ventricular end systolic and diastolic volume changes during the study**

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

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

The mass of left ventricular myocardium, which is a measure of heart volume index, reliably increased in patients of 1<sup>st</sup> group compared to the beginning of the study, indicating that left ventricular hypertrophy continues rapidly, while in 2<sup>nd</sup> group, this indicator changed in unreliable values. In 3<sup>rd</sup> 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 1<sup>st</sup> group of patients, decreasing in reliable values during our study. In the 2<sup>nd</sup> 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 3<sup>rd</sup> 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).



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

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

The formation of vascular pathology in patients with SSD 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 SSD patients of different ages, in the group of SSD patients aged 18-30 years, the thickness of the IMC was  $0.92 \pm 0.05$  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 SSD, the thickness of IMC was  $0.99 \pm 0.06$  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 SSD, the thickness of IMC was determined to be  $1.08 \pm 0.06$  mm, and the result was confirmed by statistical analysis as a reliable ( $p < 0.01$ ) thickening compared to the control group.

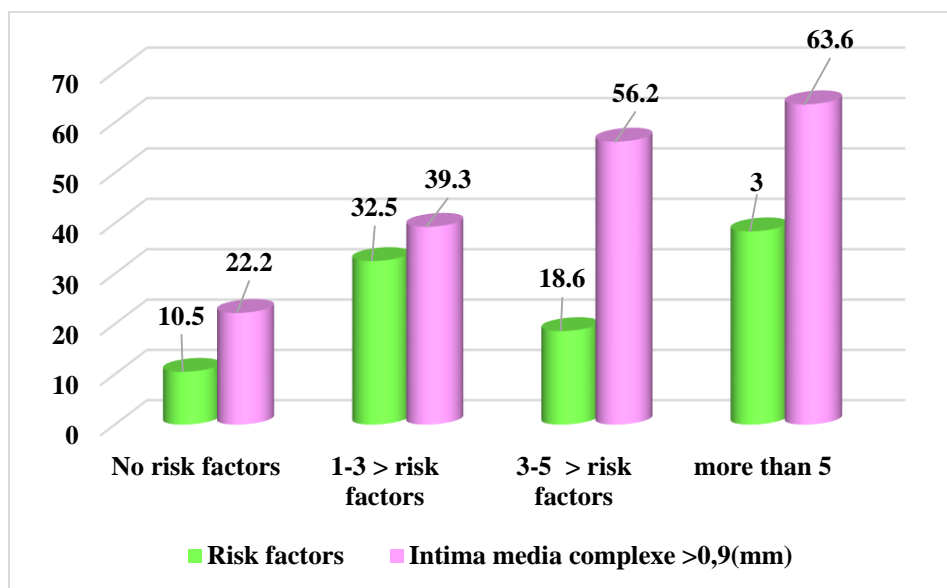
This part of our scientific research shows that in patients with SSD, one of the main risk factors of early atherosclerosis, IMC begins to thicken compared to the norm, even in patients of the age group. This is explained by the fact that when we divided our patients with SSD into three groups according 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 intima-media complex in patients and the control group by age**

Indicators	Control group (n-30)	Patients with SSD n-86		
		18-30 years n-25	31-40 years n-32	41-50 years n-29
Intima media complex of carotid arteria (mm)	0,77±0,03	0,87±0,05*	0,99±0,06**	1,08±0,06**

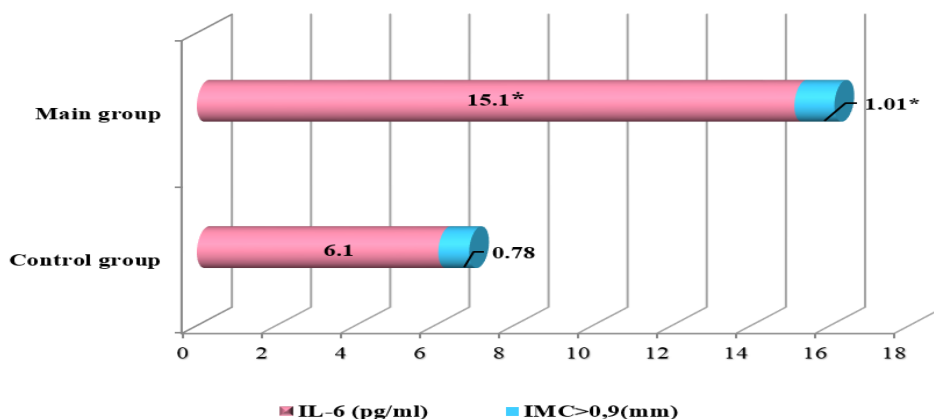
Note: \* - differences are significant compared to the indicators of the control group (\* - p<0.05, \*\* - p<0.01)

When studying the association of IMC indicators with the frequency of occurrence of risk factors (RF) in patients with SSD, 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**

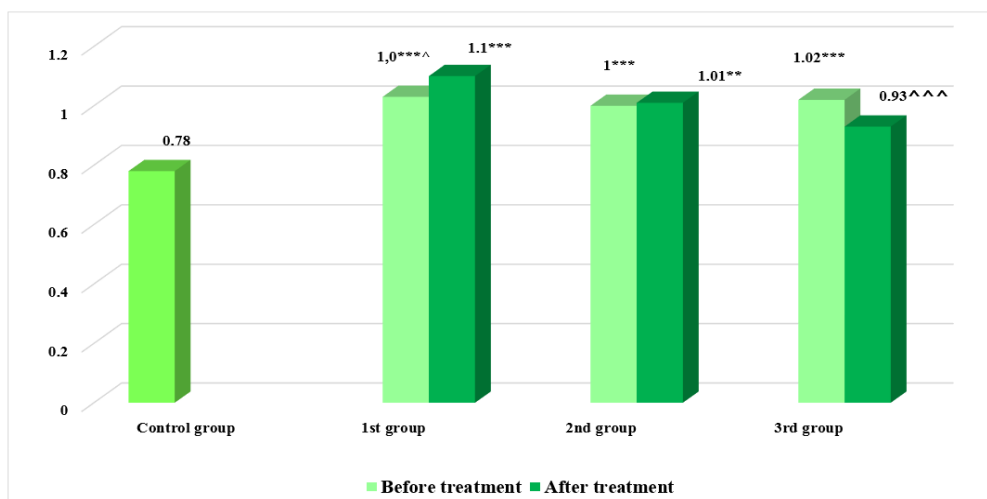
When studying the change of IL-6 in relation to the IMC indicator, compared to the control group, it was observed that the thickness of IMC exceeded 0.9 mm with an increase in the interleukin-6 content in the main group, and this value was 1 mm on average (Fig. 4).



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

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

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 1<sup>st</sup> group, the thickness of IMC showed a worsening of the process even though it was at less reliable (p<0.05) values. In 2<sup>nd</sup> group, the values did not change. In patients of 3<sup>rd</sup> 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).



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

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).



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 3<sup>rd</sup> 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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