



Effectiveness of immunosuppressive therapy for lymphocytic myocarditis according: data from actual clinical practice

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Aim. To compare the effectiveness of standard heart failure therapy with and without combined immunosuppressive therapy in patients with documented lymphocytic myocarditis (LM) based on data from actual clinical practice.

Material and methods. This observational study included 70 patients with documented LM, 40% (n=28) of whom received immunosuppressive therapy. All patients underwent standard echocardiographic and laboratory investigations, endomyocardial biopsy with histological, immunohistochemical and molecular genetic analysis. Contrast-enhanced cardiac magnetic resonance imaging was performed in 74% of patients. All patients received standard therapy for heart failure at baseline.

Results. The groups did not differ in demographic and echocardiographic characteristics. The appointment of immunosuppressive therapy was accompanied by an increase in ejection fraction by 12,2% compared to 6,4% (p=0,02). There were no significant differences in combined endpoints (survival and the need for heart transplantation) depending on therapy regimen (log-rank p=0,97).

Conclusion. The prognosis of patients with chronic LM depends on the process activity, the severity of impaired hemodynamics and ventricular arrhythmias, as well as on the presence of persistent viral infection. Compliance with patient selection algorithm before prescribing immunosuppressive therapy is associated with the improvement in myocardial global contractility.

Keywords: myocarditis, immunosuppressive therapy, prognosis.

Relationships and Activities. The study was carried out within the State Assignment of the Russian Ministry of Health "Transcriptomic biosignatures of peripheral blood cells for the prognosis of non-coronary myocardial disease course" № A20-120092490041-0.

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Myocarditis remains one of the most difficult diagnoses not only due to mosaic and nonspecific clinical manifestations of the disease, but also due to a rather complicated algorithm of diagnosis confirmation, often requiring a lifetime endomyocardial biopsy (EMB) for its verification and choice of optimal treatment method. Most patients diagnosed with acute myocarditis respond to standard therapy for heart failure (HF) and/or antiarrhythmic therapy. The analysis of two-year dynamic follow-up of patients with morphologically documented myocarditis in Charite clinic shows that left ventricular (LV) ejection fraction (EF) did not initially decrease in 26% of cases, in 27% of cases it recovered by the 2nd year of follow-up, and in 34% of patients it improved against standard therapy of HF [1]. However, the course of acute myocarditis can change rapidly. Therefore, patients with suspected myocarditis and elevated troponin levels or electrocardiogram changes should be hospitalized. Often, when hospitalized in patients with severe myocarditis, alternative therapies and, in particular, immunosuppressive therapy are used. However, most experts believe that immunosuppressive therapy in patients with acute and fulminant myocarditis should be discussed only after histological and immunohistochemical verification of the diagnosis of such rare forms of myocardial inflammatory diseases as giant cell, eosinophilic, granulomatous and autoimmune myocarditis [2]. The latter is usually associated with systemic connective tissue diseases. For other forms of inflammatory myocardial disease, the situation is more complicated. The results of the only multicenter clinical trial of MTT (Myocarditis Treatment Trial), which included 111 patients with systolic LV dysfunction and morphologically documented lymphocytic inflammation out of 2233 patients with suspected myocarditis, have not confirmed a positive effect of immunosuppression therapy on the combined endpoint (patient survival rate and need for heart transplant) and global myocardial contractility [3]. However, the active introduction of immunohistochemical and molecular genetic methods for the EMB analysis made it possible to formulate the basic principles of selecting patients for immunosuppressive therapy: disease duration ≥ 3 months, presence of LV systolic dysfunction, histological and immunohistochemical criteria of myocarditis, as well as absence of viral genome. But in real clinical practice it is rarely possible to implement the proposed algorithm, which is clearly demonstrated by the discussion that has developed around the Russian recommendations for the management of patients with myocarditis.

The present study goal: on the basis of real clinical practice data, to carry out a comparative analysis of

the efficacy of standard HF therapy without and in combination with combined immunosuppressive therapy in patients with morphologically documented lymphocytic myocarditis (LM).

Material and methods

Between 2017 and 2020, the observational study included 70 patients aged 18-64 years (66% men) with documented LM (number of CD3⁺ cells in myocardial biopsy samples 18 [15; 22] per mm²) and disease duration >3 months who were treated at the V.A. Almazov Scientific Research Center. The study protocol was approved by the Center's local ethics committee. All studies involving individuals was performed in accordance with the Declaration of Helsinki after signing informed consent. We used diagnostic criteria of myocardial inflammatory disease proposed by the European Society of Cardiology expert group for the enrollment [2].

All patients, according to the current recommendations, were treated for the correction of HF symptoms and/or rhythm disturbances [4, 5]. Along with basic therapy, immunosuppressive therapy, both as monotherapy with glucocorticosteroids and in combination with cytostatic drugs, was prescribed to 40 percent of patients, guided by history, clinical course and morphological analysis of EMB. In prescribing hormonotherapy, we followed the regimen proposed in the TIMIC study: prednisolone at 1 mg/kg per day for 1 month, followed by a decrease of 0,33 mg/kg for 5 months [6].

All patients underwent a standard echocardiographic (Echo) examination on Vivid 7 device (GE, USA) at the time of diagnosis verification and again after 7 [5; 12] months. Cardiac magnetic resonance imaging (MRI) with contrast enhancement (Gd-DO3A 0,2 ml/kg body weight) was performed on high-field Magnetom Trio A Tim 3.0T (Siemens) in 74% of patients. Every third patient subsequently underwent a control MRI examination. Lake Louise consensus criteria were used to assess inflammatory changes in myocardium: focal or global enhancement of MR signal intensity on T2-VI, increase of global early myocardial contrast enhancement coefficient and presence of late contrast enhancement foci in myocardium [7]. Patients with intermediate and high pretest probability underwent coronary angiography (n=42). As additional methods of investigation, the patients underwent daily electrocardiogram monitoring, determination of C-reactive protein level on automatic biochemical analyzer "CobasIntegra 400+" by turbidimetric method, assessment of serum concentration of N-terminal brain natriuretic propeptide (NT-proBNP) by electrochemiluminescent method on Elecsys analyzer (Roche Diagnostic) and troponin I by immunoassay method.

Table 1

Clinical characteristics of patients in the study groups

	Group with immunosuppressive therapy, n=28	Group without immunosuppressive therapy, n=42	
Age, years	38,7±14,0	40,4±11,9	0,59
Gender, m:w	15:13	31:11	0,08
Body mass index, kg/m ²	24,7±5,6	26,1±6,2	0,34
Smoking, n (%)	15 (54)	23 (55)	0,92
Infection suffered in the last 12 months, n (%)	16 (57)	23 (55)	0,84
Autoimmune diseases, n (%)	2 (7)	9 (21)	0,11
Time from the moment of the first clinical symptoms to the diagnosing, days	104 [24; 255]	93 [34; 295]	0,96
Disease onset			
Pain syndrome, n (%)	9 (32)	17 (41)	0,48
Symptoms of heart failure, n (%)	24 (86)	36 (86)	1,00
FC III/IV (NYHA), n (%)	22 (79)	29 (69)	0,38
Cardiogenic shock, n (%)	6 (21)	2 (5)	0,03
Systemic hypotension, n (%)	14 (50)	7 (17)	<0,01
Rhythm and/or conduction disturbances			
Atrial fibrillation/flutter, n (%)	6 (21)	12 (29)	0,50
Ventricular tachycardia, n (%):	19 (68)	27 (64)	0,76
— unstable, n (%)	6 (21)	18 (43)	0,06
— stable, n (%)	13 (46)	9 (21)	0,03
Echo parameters			
Longitudinal LA size, mm	45,1±8,2	46,5±7,3	0,48
LV EDD, mm	62,6±10,3	66,5±11,5	0,15
LV ESD, mm	52,9±9,5	54,5±14,4	0,62
LV ejection fraction, %	28,5±11,6	30,7±11,4	0,43
RV parasternalnaya position, mm	31,9±6,8	32,8±5,2	0,51
TAPSE, mm	16,9±4,7	18,3±3,2	0,17
Systolic pressure in pulmonary artery, mmHg	36,8±10,5	38,3±9,8	0,52
Heart MRI parameters:			
	n=21	n=31	
LV EF, n (%)	31,6±12,2	27,5±13,2	0,34
Myocardial edema by T2WI, n (%)	11 (52)	8 (26)	>0,05
LGE, n (%)	20 (95)	30 (97)	0,77
Drug therapy:			
BB + ACE inhibitors/AIIRA, n (%)	27 (96)	38 (91)	0,34
BB + ACE inhibitors/AIIRA + diuretics, n (%)	22 (79)	33 (79)	0,71
Inotropic drugs, n (%)	10 (36)	6 (14)	0,04
Immunoglobulins, n (%)	9 (32)	10 (24)	0,44
Disease outcomes:			
Heart transplantation, n (%)	5 (18)	2 (5)	0,07
Fatal outcome, n (%)	1 (4)	4 (10)	0,34

Abbreviations: AIIRA — angiotensin II receptor blocker, ACE inhibitors — angiotensin-converting enzyme inhibitors, BB — beta-blockers, EDD — end-diastolic dimension, ESD — end-systolic dimension, LV — left ventricle, LP — left atrium, MRI — magnetic resonance imaging, RV — right ventricle, EF — ejection fraction, FC — functional class, Echo — echocardiography, T2WI — T2 weighted image, LGE — late contrast enhancement, NYHA — New York Heart Association, TAPSE — tricuspid annular plane systolic excursion.

Table 2

Data of standard laboratory examination and results of histological, immunohistochemical and molecular biological examination of myocardial biopsy specimens

	Group with immunosuppressive therapy, n=28	Group without immunosuppressive therapy, n=42	p
Necrosis/dystrophy of cardiomyocytes, n (%)	24 (86)	18 (43)	<0,01
Fibrosis, n (%)	20 (71)	35 (83)	0,23
CD3 ⁺ cells/mm ² , Me (Q25-Q75)	21 [16; 34]	17 [14; 20]	0,06
≥30 CD3 ⁺ -cells, n (%)	7 (25)	2 (5)	0,01
CD68 ⁺ T-lymphocytes, cells/mm ² , Me (Q25-Q75)	16 [7; 23]	17 [12; 24]	0,47
HLA-DR 1:4	3 (3; 4)	3 (3; 4)	0,48
Viral genome, n (%):	13 (46)	21 (50)	0,77
— Enterovirus, n (%)	9 (32)	13 (31)	0,92
— Herpes virus type 6, n (%)	0	4 (10)	0,09
— Parvovirus, n (%)	10 (36)	11 (26)	0,39
Laboratory data			
Increase in troponin I ng/ml, n (%)	10 (35)	7 (17)	0,09
NT-proBNP, pg/ml	2091 [678; 3861]	1490 [365; 4928]	0,81
C-reactive protein, mg/l	2,8 [1,2; 4,1]	4,2 [1,5; 16,0]	0,12

Abbreviations: HLA-DR — antigen of the main histocompatibility complex of class II, NT-proBNP — N-terminal brain natriuretic peptide.

All patients underwent EMB before starting therapy. Repeated morphological examination was required in 14 patients receiving immunosuppressive therapy and one patient on standard HF therapy. Myocardial biopsy specimens were fixed with 10% buffered formalin. Paraffin sections of 2–3 microns were stained with hematoxylin-eosin, van Gieson with elastic trichrome to detect fibrotic changes in myocardium; toluidine was stained with blue and azure-eosin for qualitative and quantitative assessment of inflammatory infiltrates. Immunohistochemical analysis of myocardial biopsy specimens was performed using specific antibodies to major histocompatibility complex class II antigens (HLA-DR, cloneLN3, Leica, 1:300) and T-lymphocyte marker (CD-3, polyclonal antibodies, DAKO, 1:800). The HLA-DR expression of 3–4 points indicated the appearance of the antigen on non-hematopoietic cells, characteristic of the autoimmune genesis of the disease. Active myocarditis was diagnosed in the presence of cardiomyocyte necrosis/dystrophy and inflammatory infiltrate including ≥7 CD3⁺-cells per mm² [2]. Morphological forms of giantocellular, eosinophilic, granulomatous inflammation, as well as LM in patients with systemic connective tissue diseases were the criteria for non-inclusion in the study. Also, patients with documented coronary artery stenosis ≥50%, hemodynamically significant valve or clinically significant comorbidities were not included in the study.

DNA of cardiotropic viruses was detected by polymerase chain reaction. Diagnosis of RNA-containing enterovirus was made by immunohistochemical analysis of myocardial biopsy specimens for VP-1 capsid protein of the virus (monoclonal antibody, Clone 5-D8/1, DAKO).

Clinical characteristics of the groups depending on the volume and nature of the therapy are presented in Table 1.

Statistical analysis was performed using applied statistical softwares IBM SPSS 23, STATISTICA 64 v10.0. The descriptive indices with an approximate normal distribution are presented as arithmetic mean (M), standard deviation (σ) and the number of features in the group (n); in other cases, they are presented as median (Me) and quartiles. The unpaired Mann-Whitney U-criterion was used to statistically test the hypotheses on equality of numerical characteristics of the sample distributions in the compared groups. To compare binary and categorical measures, Fisher's exact two-sided criterion was used. The long-term follow-up period was up to 2 years: 350 [206; 593] days. Combined endpoint: survival and need for heart transplantation — was assessed by the Kaplan-Meier method. Survival in the two groups was compared using a log-rank test. Predictive models were built using binary logistic regression methods and ROC-analysis. Testing of statistical hypotheses was performed at the critical level of significance $p < 0,05$.

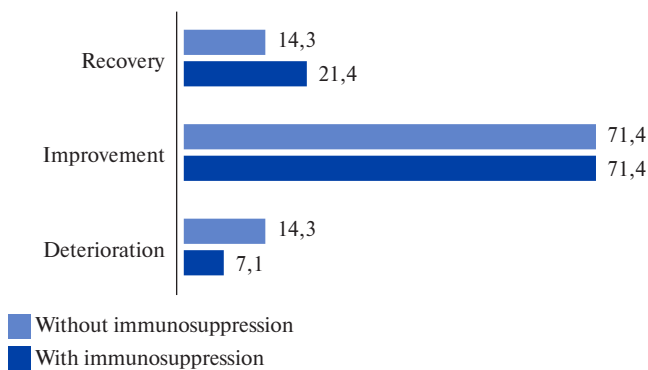


Figure 1. Dynamics of LV EF during follow-up depending on drug therapy nature.

Results

According to clinical and anamnestic data and instrumental examination data, episodes of sustained ventricular tachycardia, systemic hypotension and cardiogenic shock were registered more frequently in the group of patients with myocarditis who received immunosuppressive therapy at the disease onset. Patients with functional class IV (FC) of HF requiring inotropic support prevailed: 57% (n=16) in the immunosuppressive therapy group and 48% (n=20) in the comparison group.

At the same time, the groups did not differ in the initial Echo parameters and the cinema-MRI data (Table 1). In the group of patients on standard therapy, MR criteria of active inflammatory process in myocardium were confirmed less frequently, which is probably associated with a large number of patients with chronic myocarditis, in which the diagnostic value of cardiac MRI is reduced [8].

Necrosis and cardiomyocyte dystrophy, indicating, according to the Dallas criteria, the presence of active myocarditis, were detected in 86% of patients treated with immunosuppressive therapy, and only in 43% of patients in the standard therapy group. According to histological and immunohistochemical analysis of myocardial biopsy specimens, the groups differed in the number of inflammatory cells infiltrating the myocardium (Table 2). Taking into account fibrous changes in myocardium, the majority of examined patients had signs of chronic myocarditis.

The viral etiology of inflammatory myocardial damage was proven in 49% of cases. In the immunosuppressive therapy group, expression of VP-1 capsid protein of enterovirus on cardiomyocytes and vessel walls was detected in 3-30% of cases, whereas the presence of enterovirus genome reached 100% in the comparison group. In this regard, all patients from the immunosuppressive therapy group were preventively treated with immunomodulatory therapy with high

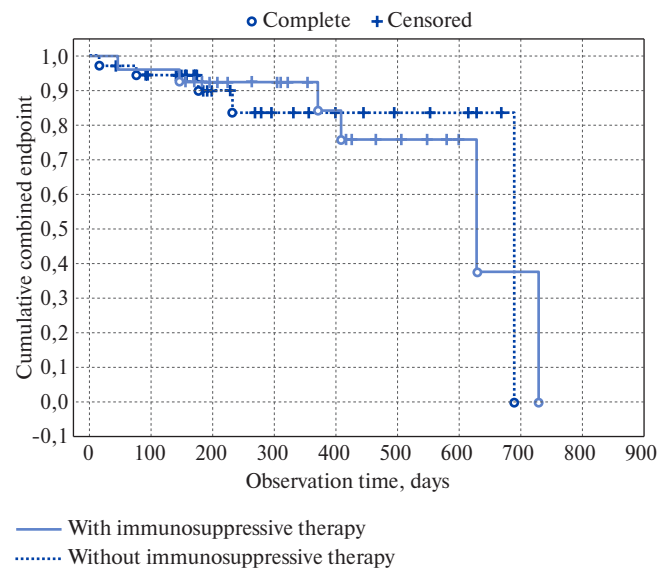


Figure 2. Cumulative survival and need for heart transplantation in patients with morphologically documented LM depending on drug therapy nature (Long-rank $p=0,97$).

doses of intravenous immunoglobulin G (daily dose 0,4 g/kg for 5 days) before the start of specific treatment. 10 patients (24%) received parenteral immunoglobulin therapy in the comparison group.

In addition, patients who received steroid therapy had elevated levels of the myocardial damage marker troponin I and higher values of NT-proBNP. Attention should be paid to the absence of an increase in the C-reactive protein level, which, as is known, does not exclude the diagnosis of myocarditis.

Initially, as part of a steroid-saving regimen, 57% of patients (n=16) received combination therapy with prednisolone combined with azathioprine 2 mg/kg (n=7) or with methotrexate 10-15 mg/week (n=5), or with mycophenolate mofetil 2 g/day (n=4). Due to the development of side effects in two patients, methotrexate and azathioprine were replaced by mycophenolate mofetil. In one case, given the high expression of CD20⁺ (marker of B-lymphocytes) in the myocardium, rituximab (500 mg/m² on day 1 and 500 mg on day 14) was prescribed in addition to standard specific therapy. 12 patients received monotherapy with prednisolone. The variability of combined immunosuppressive therapy regimens did not fundamentally affect disease outcome ($p=0,436$).

The analysis of the total sample showed an increase in EF by an average of 8,3%. In the immunosuppressive therapy group, EF increased from $28,5 \pm 11,6\%$ to $40,8 \pm 10,6\%$ compared with the group of patients receiving only standard HF therapy: from $30,7 \pm 11,4\%$ to $37,1 \pm 11,3\%$, $p=0,02$. Depending on the dynamics of myocardial contractility, patients were divided into three groups:

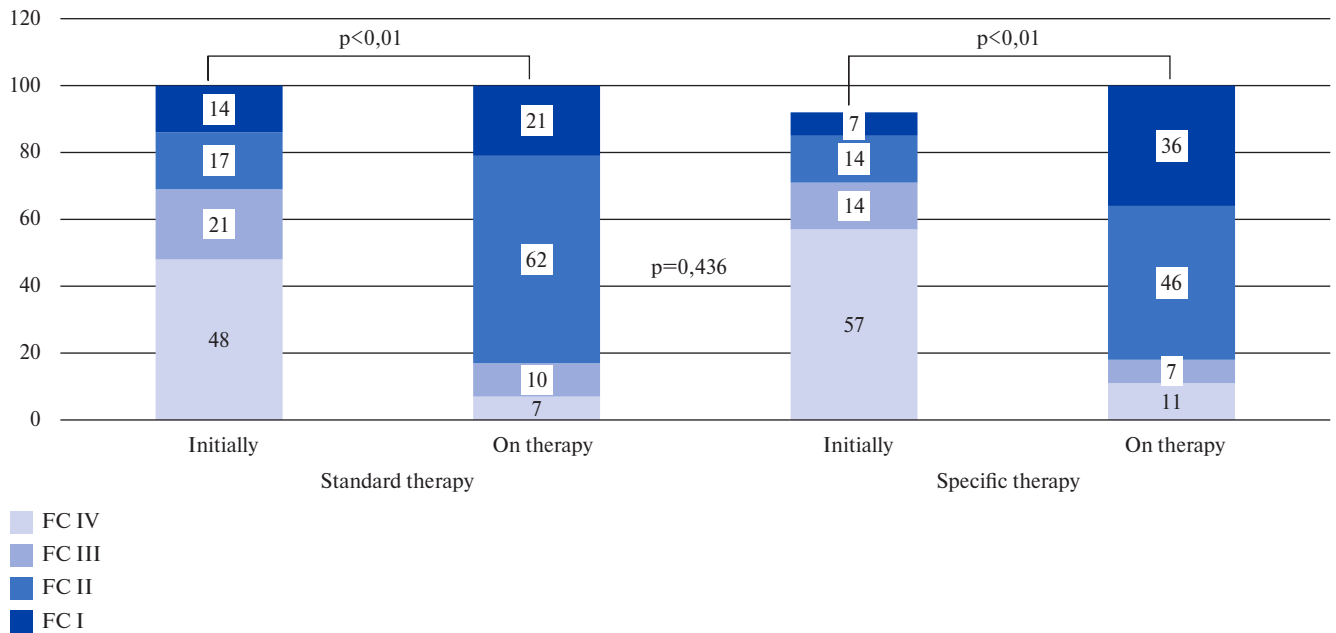


Figure 3. Dynamics of HF FC depending on therapy nature.

Abbreviation: FC — functional class.

Table 3

Logistic regression model for predicting a favorable increase in myocardial contractility

	V	Mean-squared error	Wald	Degrees of freedom	Significance	Exp (B)	95% confidence interval for EXP (B)	
							Lower	Upper
Immunosuppressive therapy	1,42	0,53	7,26	1	0,007	4,15	1,48	11,69
Active myocarditis	0,89	0,66	1,82	1	0,178	2,42	0,67	8,78
Virus	-0,64	0,47	1,88	1	0,171	0,53	0,21	1,32
Signs of chronization	-0,45	0,62	0,54	1	0,464	0,64	0,19	2,13

1) *recovery* was interpreted as an increase in EF of >50%; 2) *improvement* — if there is a positive dynamic, but without reaching EF >50%; 3) *deterioration* was defined as a decrease in EF in the process of observation (Figure 1).

The combined endpoint analysis (survival rate and need for heart transplantation) did not reveal any significant effect of immunosuppressive therapy on the long-term prognosis of patients with LM compared to standard therapy for HF (Figure 2). There was a more favorable prognosis in patients with EF >40% at the time of diagnosis, whereas patients with initially low fraction were more likely to have a severe course of the disease, leading to heart transplantation and/or death ($p=0,04$). In the course of treatment, HF FC decreased both in the group of standard therapy ($p<0,01$) and in the group of patients who received additional immunosuppressive therapy ($p<0,01$) (Figure 3).

Using ROC analysis, the threshold value of EF associated with a favorable prognosis of the myocarditis

course was determined (AUC 0,77, 95% confidence interval 0,63-0,91, $p=0,03$). In our study, it was +12%. After step-by-step regression, the most informative risk factors were selected: immunosuppressive therapy, inflammatory activity, presence of viral genome and signs of chronic inflammatory process. Of the above factors, the use of immunosuppressive therapy proved to be the most significant predictor of a favorable outcome of LM (Table 3). The presence of active myocarditis positively correlated with an increase in EF during treatment, whereas the presence of fibrotic changes and persistent viral infection negatively influenced the long-term results of treatment.

Discussion

HF therapy remains the cornerstone of treatment of patients with inflammatory myocardial disease accompanied by systolic dysfunction. In foreign literature, this pathology is often referred to as “inflammatory cardiomyopathy” [1, 2]. To date, such disease-modifying drugs as angiotensin-converting

enzyme inhibitors/angiotensin II receptor antagonists and beta-adrenoblockers, due to their pleiotropic anti-inflammatory and anti-apoptotic effects, have proven effective as basic therapy for patients with myocarditis. This is also evidenced by the results of our study, in which the two-year survival rate without heart transplantation and the dynamics of functional status of patients did not depend on the regime of the chosen therapy. In contrast, in a recently published study by Merken J, et al, who analyzed the treatment outcomes of 209 patients with virus-negative LM, the administration of immunosuppressive therapy was accompanied by improved survival of patients without heart transplantation (Long-rank $p=0,043$, hazard ratio 0,34, 95% confidence interval 0,17-0,92) [9]. However, it should be noted that, unlike our sample, in this study, among patients with EF=33%, >60% of patients had CH FC I-II. This point is particularly important because it once again emphasizes the need to exploit the potential of standard therapy for CH before discussing the prescription of immunosuppressive drugs, especially when it comes to patients with chronic LM. The next equally important point — the detection of viral genome. It is still an open question whether a persistent viral infection is the initiator of the pathological process or a bystander. The literature often mentions latent infections caused by herpes viruses or parvovirus B19 [1]. The situation in real clinical practice in Russia is further complicated by the fact that there are no validated test systems designed for the quantification of viral copies in myocardial biopsy specimens. The qualitative assessment (immunohistochemical assay for VP-1 capsid protein of enterovirus), that was used in our study, does not warrant discussion of antiviral therapy before prescription of immunosuppressive drugs. In addition, the possibility of using a combination of antiviral and immunosuppressive drugs in selected patients with virus-positive inflammation is still the subject of debate. The only exception that allows discussing the use of immunosuppressive drugs without prior antiviral therapy may be parvovirus infection, especially when the viral load is low [10]. In this connection, preliminary results of CAPACITY (Cortisone in PARvovirus inflammatory cardiomyopathy) study, demonstrating resolution of inflammation and improvement of EF against the background of immunosuppressive therapy in patients with parvovirus inflammatory cardiomyopathy, look optimistic [11].

In recent years, the possibility of using intravenous immunoglobulins as an alternative approach for detecting latent viral infection has been increasingly discussed, focusing on the positive anti-inflammatory effects of the drugs, immune system activation and opsonization of infectious agents [12].

However, the Russian recommendations for the management of patients with myocarditis referred this class of drugs to level III.

Viral infection initiates autoreactive cellular and humoral immune response. Additional evidence of the autoimmune nature of myocarditis is the persistent myocardial inflammation in the absence of an infectious agent, increased titers of circulating cardiac-specific autoantibodies, and HLA-DR expression on nonhematopoietic cells. In the absence of a viral genome, the efficacy of immunosuppressive therapy also indicates the role of autoimmunity disorders in the pathogenesis of myocardial inflammatory diseases. The improvement of global LV contractility demonstrated in the present study and in a number of other publications once again emphasizes the promise of prescribing immunosuppressive therapy in patients with chronic LM [13]. However, the results of metaanalysis of 8 randomized clinical trials have shown that immunosuppressive therapy does not significantly affect mortality and the need for heart transplantation, but is accompanied after 1-3 months by a significant increase in LV EF by 7%, and in one study with long-term follow-up — by 13% [14]. The explanation should be sought in mosaic nature of myocarditis: the activity variability of pathological process, the influence of hemodynamic disorders and the presence of life-threatening rhythm disturbances on the outcome of the disease, as well as the role of latent viral infection in modulating the expression of genes involved in the pathological process of myocardial structural changes.

Conclusion

The analysis of real clinical practice showed the importance of following the recommendations of standard therapy of HF in patients with LM. Although the administration of immunosuppressive therapy had no effect on survival/need for heart transplantation, adherence to the algorithm for selecting patients for this type of therapy was accompanied by an improvement in global myocardial contractility. The use of intravenous immunoglobulins offers additional opportunities in the treatment of patients with LM. A multicenter clinical trial is needed to resolve a number of debatable issues that arise in prescription of immunosuppressive therapy to answer the question on place of this type of therapy in the treatment of patients with LM.

Relationships and activities. The study was performed within the State Assignment of the Ministry of Health of the Russian Federation “Transcriptomic biosignatures of peripheral blood cells for evaluation of prognosis of the course of noncoronary myocardial diseases” No. A20-120092490041-0.

References

1. Tschöpe C, Cooper LT, Torre-Amione G, et al. Management of Myocarditis-Related Cardiomyopathy in Adults. *Circulation Research*. 2019;124(11):1568-83. doi:10.1161/CIRCRESAHA.118.313578.
2. Caforio AL, Pankuweit S, Arbustini E, et al. European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *European Heart J*. 2013;34(33):2636-48, 2648a-2648d. doi:10.1093/eurheartj/ehd210.
3. Hahn EA, Hartz VL, Moon TE, et al. The Myocarditis Treatment Trial: design, methods and patients enrollment. *European Heart J*. 1995;16(Suppl O):162-7. doi:10.1093/eurheartj/16.suppl_o.162.
4. Mareev VY, Fomin IV, Ageev FT, et al. Russian Heart Failure Society, Russian Society of Cardiology. Russian Scientific Medical Society of Internal Medicine Guidelines for Heart failure: chronic (CHF) and acute decompensated (ADHF). Diagnosis, prevention and treatment. *Kardiologiia* 2018;58(6S):8-158. (In Russ.) doi:10.18087/cardio.2475.
5. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC) Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *EP Europace*. 2015;17(11):1601-87. doi:10.1093/europace/euv319.
6. Frustaci A, Russo MA, Chimenti C. Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. *European Heart J*. 2009;30(16):1995-2002. doi:10.1093/eurheartj/ehp249.
7. Ferreira VM, Schulz-Menger J, Holmvang G, et al. Cardiovascular Magnetic Resonance in Nonischemic Myocardial Inflammation: Expert Recommendations. *J Am College of Cardiology*. 2018;72(24):3158-76. doi:10.1016/j.jacc.2018.09.072.
8. Ignatieva ES, Ryzhkova DV, Mitrofanova LB, et al. Magnetic resonance imaging of the heart in diagnostics of various types of myocarditis. *Russian Journal of Cardiology*. 2017;(2):30-8. (In Russ.) doi:10.15829/1560-4071-2017-2-30-38.
9. Merken J, Hazebroek M, Van Paassen P, et al. Immunosuppressive Therapy Improves Both Short- and Long-Term Prognosis in Patients With Virus-Negative Nonfulminant Inflammatory Cardiomyopathy. *Circulation: Heart Failure*. 2018;11(2):e004228. doi:10.1161/CIRCHEARTFAILURE.117.004228.
10. Sinagra G, Porcari A, Gentile P, et al. Viral presence-guided immunomodulation in lymphocytic myocarditis: an update. *European J Heart Failure*. 2021;23(2):211-6. doi:10.1002/ehfj.1969.
11. Tschöpe C, Elsanhoury A, Schlieker S, et al. Immunosuppression in inflammatory cardiomyopathy and parvovirus B19 persistence. *European J Heart Failure*. 2019;21(11):1468-9. doi:10.1002/ehfj.1560.
12. Maisch B, Alter P. Treatment options in myocarditis and inflammatory cardiomyopathy: Focus on i.v. immunoglobulins. *Herz*. 2018;43(5):423-30. doi:10.1007/s00059-018-4719-x.
13. Maisch B, Pankuweit S. Inflammatory dilated cardiomyopathy: Etiology and clinical management. *Herz*. 2020;45(3):221-9. doi:10.1007/s00059-020-04900-8.
14. Chen HS, Wang W, Wu SN, et al. Corticosteroids for viral myocarditis. *Cochrane Database Syst Rev*. 2013;2013(10):CD004471. doi:10.1002/14651858.CD004471.pub3.