

Stem cell therapy of myocarditis and cardiomyopathies: a promising strategy



Kovalenko V., Nesukay E., Cherniuk S.*, Kozliuk A.

M. D. Strazhesko National Scientific Center of Cardiology, Clinical and Regenerative Medicine, National Academy of Medical Sciences of Ukraine», Kyiv, Ukraine

*Corresponding author's e-mail: cerniuk.sergey@gmail.com

ABSTRACT

The review is devoted to the analysis of modern data on the effectiveness of stem cell transplantation in patients with non-coronary heart diseases: myocarditis, dilated cardiomyopathy, and systemic amyloidosis with heart involvement. The results of experimental studies on laboratory animals and clinical trials concerning the use of various types of stem cells, their mechanisms of action and prospects for application in non-coronary heart diseases are given. Emphasis is placed on the need for further randomized multicenter clinical trials, especially in patients with inflammatory myocardial damage, involving a large number of patients.

KEY WORDS: stem cells; cell therapy; dilated cardiomyopathy; myocarditis; amyloidosis

In the last decade, more and more reports have appeared in the scientific literature about the prospects of using stem cells (SCs) in the complex therapy of non-coronary heart diseases. The obtained positive results apply not only to experimental studies on laboratory animals, but also to studies in the field of clinical cardiology. In the era of evidence-based medicine, the effectiveness of therapy with SCs transplantation (SCT) is actively studied in patients with a wide range of cardiac pathologies: coronary heart disease (CHD), heart failure (HF) of various geneses, chronic diffuse myocarditis (inflammatory cardiomyopathy), dilated cardiomyopathy (DCM), as well as various phenotypes of restrictive cardiomyopathy, in particular associated with cardiac amyloidosis. The literature review is devoted to the analysis of the latest data related to the pathogenesis basis of the regenerative effect of SCs, the results of experimental studies and the possibilities of using cell therapy in clinical practice for non-coronary heart diseases.

Types of stem cells and their effects

The prospects of SCs application for regenerative therapy in cardiovascular diseases, in particular non-coronary heart diseases, are related to their physiological effects. As it is known, myocarditis, DCM and other non-coronary heart diseases are characterized by a progressive course with gradual replacement of the contractile apparatus of the heart muscle by connective tissue, which leads to a violation of the contractile ability of the myocardium, systolic dysfunction and dilatation of the heart. The main effects of SCs that stimulate the recovery of myocardial tissue are their ability to differentiate into cells similar to cardiomyocytes, reduce the inflammation, which is very relevant in myocarditis, antiapoptotic and antifibrotic activity, as well as in the stimulation of angiogenesis [12].

According to modern concepts, SCs are divided into two types – embryonic and adult stem cells. Adult SCs, in turn, are divided into the following types depending on their origin: SCs from bone marrow, adipose tissue, umbilical cord, skeletal muscles, placenta, lungs, heart tissues,

and pluripotent SCs, and most of the listed types have undergone experimental or clinical studies as regenerative therapy for various cardiovascular pathologies, including non-coronary heart diseases [12, 29].

Mesenchymal stem cells (MSCs) derived from bone marrow, adipose tissue, umbilical cord and placenta are widely used in clinical studies. Currently, leading specialists in the field of regenerative medicine consider MSCs as the main source for cell therapy in inflammatory, degenerative, and autoimmune diseases [12, 20, 42]. The figure shows the main effects of MSCs, which determine the perspective of their use as cellular product in cardiology and their preparation for transplantation.

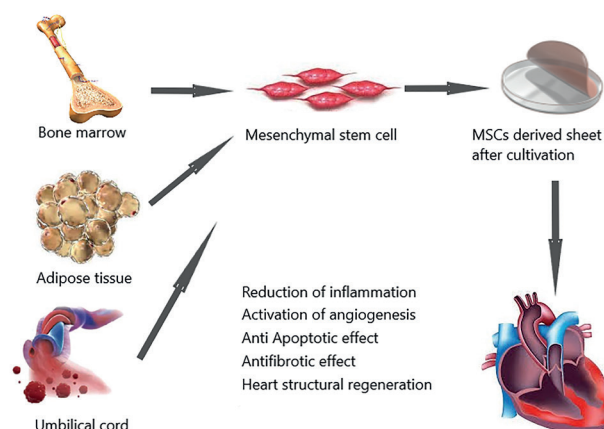


Fig. 1. Sources and main effects of mesenchymal stem cells in cardiac pathology

According to the results of the PERFECT study, the use of hematopoietic SCs in an experimental model of myocardial infarction was associated with an increase in capillary density and, as a result, an improvement in the vascularization of the myocardium, a reduction in fibrotic lesions and an improvement in the systolic function of the heart, and in a parallel clinical trial – with an increase in the left ventricular ejection fraction (LVEF) and improvement of myocardial perfusion according to MRI data [44].

On the other hand, it is necessary to take into account the reports of cardiotoxicity of hematopoietic SCs. In several studies it was shown that the risk of cardiomyopathy development increases against the background of long-term use of such therapy, especially in cases of the presence of associated genes, arterial hypertension, CHD and disease progression as well as conditions related to metabolic syndrome [8, 23].

SCs obtained from adipose tissue have a wide range of application, primarily in experimental studies, which is due to the relative ease of their isolation from adipose tissue during liposuction. Despite the fact that SCs of adipose origin have many common characteristics with MSCs of bone marrow origin, to date, there is no unified scientific opinion as to whether adipose-derived SCs can be classified as MSCs, however, most authors distinguish them as a unique type of progenitor cells [18]. SCs of adipose origin have already proven their effectiveness in randomized clinical trials in patients with coronary artery disease. For example, in the MyStromal-Cell trial, it was shown that their administration is accompanied by an improvement in exercise tolerance and a reduction in the symptoms of stable angina pectoris. In the APOLLO study, the use of adipose-derived SCs led to a reliable increase in EF and improvement in LV perfusion [15, 33]. It is obvious that the use of this type of SCs may have prospects for patients with non-coronary heart diseases. For example, data was recently obtained indicating the effectiveness of adipose-derived SCs administration to animals with experimental DCM, which was manifested in the activation of the expression of cardiac myosin and an increase in the concentration of ATP due to the stimulation of adenine nucleotide translocase type 1 [27].

The use of SCs derived from skeletal muscles for regenerative therapy has long been considered promising, since these cells have the ability to differentiate into myotubular structures, which should reduce the heart remodeling and improve its systolic function. However, the results of experimental and small clinical studies were not as promising as it was believed at the preclinical stage, due to pro-arrhythmogenic effects with the occurrence of ventricular arrhythmias as a result of a violation of the electromechanical interaction between the cells of the regenerated myocardium [29]. As a result, the use of skeletal muscle SCs is limited for regenerative therapy in cardiomyopathies both in experimental models and in clinical studies.

Embryonic SCs are obtained from undifferentiated inner cell mass of human blastocyst. Both in experimental models and in clinical practice, these cells have a wide range of application points for cell therapy, as they are pluripotent and can differentiate into cells that will later form various tissues and organs, including cardiomyocytes. In an experimental model on laboratory rats, it was shown that the transplantation of human induced pluripotent SCs capable of differentiating into cardiomyocytes increases the tolerance of the myocardium to hypoxia, improves its contractile function, and activates the restoration of the cytoskeleton and membrane matrix by stimulating the synthesis of desmin and dystrophin [47]. The effects of induced pluripotent SCs revealed in this study were noted on the ischemic heart; however, the described restorative processes have great prospects for non-coronary heart diseases, primarily for DCM and chronic myocarditis. However, in many countries their research has limitations due to ethical considerations, the uncertainty of the genetic consequences of their use, and because of high immunogenicity and the frequent development of teratomas [29].

Stem cell therapy for DCM

The use of MSCs in experimental models of DCM began more than 2 decades ago. *Ex vivo*, MSCs have been shown to be able to activate

angiogenesis and myogenesis by synthesizing a large number of proangiogenic, mitogenic, and antiapoptotic factors, such as vascular endothelial growth factor, adrenomedullin, and insulin-like growth factor-1 [14, 17, 20]. In addition, it was shown that after MSCs transplantation, the synthesis of cardiac smooth muscle actin, cardiac desmin, troponin T, connexin-43 and structural elements responsible for myocardial vascularization is activated [28]. These processes are the physiological basis for the inhibition of fibrosis and the gradual replacement of fibrotic tissue by contractile and vascular structures, which is accompanied by a decrease in dilatation and restoration of the contractility of the LV in laboratory animals with experimental DCM [12, 14, 28]. At the same time, in experimental models of DCM, it was shown that the administration of human umbilical cord blood MSCs to rats reduces the activity of fibrosis in the myocardium by inhibiting the synthesis of collagen type I and III, reducing the profibrotic activity of transforming growth factor- β , the content of tumor necrosis factor- α (TNF- α), as well as other connective tissue growth factors [49].

One of the first clinical studies that demonstrated the effectiveness of bone marrow mononuclear SCs transplantation in patients with DCM was a study performed by S. Seth and co-authors, which included 85 patients with reduced LVEF without coronary arteries stenosis [36]. During the 3-year follow-up of 45 patients who underwent the transplantation of autologous SCs, the authors established that LVEF significantly increased by 5.9% after cell therapy compared to the control group. The functional class of HF according to New York Heart Association (NYHA) and the quality of life of patients according to the Kansas City Cardiomyopathy Questionnaire (KCCQ) improved. Nevertheless, there was no significant difference in the mortality rate and LV end-diastolic volume in comparison with the control group of 40 patients with DCM who did not receive cell therapy. According to the results of endomyocardial biopsy in 8 patients who underwent SCs transplantation, an improvement in the vascularization of the myocardium and an increase in the density of the capillary network were noted, however, no signs of transdifferentiation of SCs into new cardiomyocytes were detected.

In another placebo-controlled randomized clinical trial conducted by J. Butler and co-authors, which included 22 patients with DCM and reduced LVEF, allogeneic MSCs were used [5]. An important condition for inclusion in the study was the absence of signs of inflammatory damage to the myocardium on cardiac MRI. According to the results, SCT had no significant effect on mortality and hospitalization rates, as well as on the improvement of contractility and reduction of LV volumes, however, compared to placebo, it improved the results of the 6-minute test and the data of the KCCQ. In addition, in the treatment group, the authors noted immunomodulatory effects of SCT, manifested in an increase in the content of CD3 and CD4 lymphocytes and a decrease in the concentration of natural killers, which was associated with an increase in LVEF.

A classic randomized clinical study that proved the effectiveness of cell therapy in patients with DCM is the POSEIDON-DCM trial, which compared the safety and effectiveness of allogeneic and autologous MSCs [12]. According to its results, transendocardial injection of allogeneic MSCs in patients with DCM was accompanied by a significant increase in LVEF and a decrease in its dilatation, an improvement in the results of the 6-minute test, a decrease in NYHA functional class of heart failure and an improvement in the results of the test according to the Minnesota questionnaire. These positive effects were maintained for at least 12 months. At the same time, in the group of patients with DCM who underwent transplantation of autologous MSCs, LVEF after a course of cell therapy was significantly lower, and the frequency of cardiovascular events was higher compared to those in the group of patients who underwent transplantation of allogeneic SCs.

Tompkins B. et al. conducted a sub-analysis of 3 clinical studies (including POSEIDON-DCM) on the effectiveness of MSCs therapy in patients with DCM in comparison with patients with ischemic cardiomyopathy. In general, the authors noted high efficiency in both groups, while in patients with DCM, the restoration of LVEF was carried out at a faster

pace, and after 12 months of observation, its value was 7 % higher [39]. The superiority of allogeneic MSCs over autologous MSCs in reducing the activity of systemic inflammation in patients with DCM is also evidenced by the results of a subanalysis in the POSEIDON-DCM study. The administration of allogeneic MSCs is accompanied by the stimulation of the formation of stromal cell-derived factor 1- α and suppression of free radical oxidation processes, as well as a decrease in the level of a powerful pro-inflammatory agent – tumor necrosis factor- α (TNF- α) [32]. Also noteworthy are the data from another subanalysis of the POSEIDON-DCM study, in which genetic testing showed that the best responders to cell therapy were patients who did not have the pathological genes associated with DCM. These patients, compared to those with DCM-associated genetic mutations or those with questionable mutations, had faster recovery of LVEF under the influence of cell therapy, had better exercise tolerance and a lower frequency of cardiovascular events [34].

In one of the studies, which included 53 patients suffering DCM with reduced LVEF, a comparative analysis of the effectiveness of intracoronary infusions of MSCs and autologous bone marrow mononuclear cells was conducted [45]. According to the results obtained, in the group of patients who underwent MSCs transplantation, in comparison with the control group, after 12 months of observation, an improvement in the parameters of the structural and functional state of the heart was noted: an increase in the value of LVEF, a decrease in the functional class of HF, and an improvement in myocardial perfusion. On the other hand, in patients who were injected with mononuclear cells, no positive dynamics were noted. Thus, results confirming the superiority of MSCs for cell therapy in patients with DCM were again obtained. However, the frequency of cardiovascular events in both the studied groups and the control group was not significantly different.

The data of a rather large-scale, as for this disease, meta-analysis, which included 7 randomized studies and 341 patients, also testify in favour of the effective use of MSCs in patients with DCM [2]. According to the obtained results, the transplantation of MSCs in addition to optimal drug therapy of HF allows not only reliably increase the value of EF, reduce LV end-diastolic volume, improve the results of the 6-minute walk test, but also ensure better survival, at least during the first 12 months of observation. However, cell therapy did not have a significant effect on the frequency of life-threatening heart rhythm disorders and did not reduce the percentage of patients who had to undergo heart transplantation.

To date, comparative studies of the effectiveness and safety of SCs therapy in patients with DCM and surgical treatment methods have also been conducted. It was established that after SCT of umbilical cord blood, as well as after partial resection of the LV (Batista procedure), the EF significantly increased and the end-diastolic volume decreased, and this trend was maintained during the first 12 months [1]. Later, the authors noted a gradual decrease in LVEF in both groups of patients almost to the initial level. However, the 12-month mortality in the group of patients who underwent the Batista procedure was 15.7 %, whereas in patients after SCT, this parameter was only 4.5 %. The authors conclude that SCT in patients with DCM can be considered as a safer alternative to surgical intervention and as a kind of bridge, which allows to improve the structural and functional condition of the LV and reduce the risk of death while waiting for heart transplantation.

Stem cell therapy for myocarditis

The use of SCs in myocarditis has shown sufficiently high efficiency in experimental models on laboratory animals, however, there is currently no information on their use in patients with viral or autoimmune myocarditis in clinical practice. In experiments on laboratory mice with myocarditis associated with the Coxsackie B3 virus, the administration of MSCs was characterized by a decrease in the level of monocytes both in the myocardial tissue and in the peripheral blood, which was accompanied by a decrease in the concentration of TNF- α , interleukin-6, and interleukin-12 [26]. The decrease in the activity of fibrosis was due to the inhibition of the expression of the transforming growth factor- β and

the decrease in the synthesis of collagen type 1 and type 3. In another experimental study, it was shown that transplanted MSCs are insensitive to the pathological effects of the Coxsackie B3 virus, and their administration in Coxsackie B3-induced myocarditis significantly inhibits the apoptosis, reduces the intensity of oxidative stress, and inhibits viral replication [41]. In addition, it was established that transplantation of MSCs in animals with experimental myocarditis is accompanied by a decrease in the level of pro-inflammatory cytokines, in particular TNF- α , and a decrease in monocyte activity, which results in a decrease in the intensity of cardiomyocytes damage, improvement in systolic and diastolic heart function [41]. It has also been proven that the transplantation of MSCs into animals with severe myocarditis, induced by the injection of cardiac myosin, significantly reduces inflammatory damage to the heart muscle due to stabilization of the endoplasmic reticulum and inhibition of apoptosis processes in cardiac cells [48].

Another approach to cell therapy of myocarditis, which is now considered promising, according to the results of experimental studies, is the intravenous administration of bone marrow MSCs exosomes. The administration of MSCs exosomes to laboratory animals was accompanied by a decrease in the activity of the inflammatory process and a decrease in the concentration of macrophages and pro-inflammatory cytokines in the myocardium and an improvement in its contractile capacity [46]. In addition, MSCs exosomes therapy significantly reduced the activity of apoptosis of cardiomyocytes and endothelial cells by regulating anti-apoptotic factors such as LC3II/I, BECLIN-1, BCL-2, as well as inhibiting the expression of pro-apoptotic proteins P62 and BAX [11]. To date, we have also received data that the administration of MSCs exosomes with overexpression of miRNA-133a into laboratory animals reduces the activity of inflammation in the myocardium, has an antifibrotic and antiapoptotic effect [24].

A promising direction in the treatment of myocarditis, which has proven its effectiveness in experimental models on laboratory animals, is the use of cells from cardiospheres, which are spheroids formed from SCs of human heart tissue *in vitro*. In one of the experimental studies, it was proved that the administration of these cells to laboratory animals with myosin-induced myocarditis is accompanied by a decrease in infiltration of the myocardium by immune cells, inhibition of inflammation and fibrosis, which results in an improvement in contractility and a decrease in LV dilatation [30].

A pathogenesis justified approach to the treatment of experimental myocarditis is the transportation of anti-inflammatory cytokines by MSCs to the area of autoimmune inflammation in the myocardium. In one study, it was shown that the administration of MSCs with hyperexpression of the anti-inflammatory interleukin-10 to laboratory animals with experimental myocarditis led to a decrease in the levels of pro-inflammatory cytokines, in particular interleukin-1 β , TNF- α , interleukin-6 and interleukin-17, as well as to a decrease in the concentration markers of cardiomyocyte lysis – troponin I and myocardial creatine phosphokinase [37]. In addition, it was noted that the transplantation of MSCs with hyperexpression of interleukin-10 is accompanied by a more pronounced decrease in myocardial infiltration by monocytes and macrophages than the administration of normal MSCs.

The only clinical study that can be indirectly attributed to the study of the effects of SCs in patients with myocarditis is the SENECA study, which included convalescents after cancer who developed inflammatory cardiomyopathy caused by anthracyclines [3]. Its final results have not yet been published, however, according to preliminary data, MSCs demonstrated a satisfactory safety profile and good tolerability, while their transplantation was accompanied by a significant increase in LVEF and longitudinal strain indicators 6 and 12 months after the start of treatment.

Today, leading scientists in the field of both clinical and fundamental cardiology recognize the need for randomized clinical trials to assess the safety and effectiveness of SCs transplantation in patients with myocarditis [12, 40, 42]. The use of cell therapy should be considered first of all in patients with severe myocarditis in cases of persistence of the inflam-

matory process in the myocardium and activation of fibrosis, especially in the case of insufficient effectiveness of anti-inflammatory therapy of HF.

Stem cell therapy in amyloidosis

Amyloid light (AL) chain or primary amyloidosis is based on the violation of the coagulation of pathological proteins synthesized by plasma cells (rarely B cells) with their deposition in organs. AL amyloidosis variants with a pronounced cardiac involvement are the most difficult cases to treat in terms of the severity of the patient's status. The use of various chemotherapeutic schemes and immunotherapy is designed to achieve a complete or partial hematological response by suppressing the pathological cell pool in the bone marrow, which allows to reduce the production of circulating light chains and cause their exit from the deposition organs. Today, it is known that the use of modern chemotherapeutic agents provides a hematological response in 50-94 % of cases, while a complete clinical response occurs only in 20-44 % of treated patients [9, 21, 43]. However, the expected effect of the treatment of the affected organs, in particular the heart, is possible only under the condition of long-term and stable elimination of circulating light chains, which is not always achieved by the use of medication alone. In such conditions, replacing the aberrant cell pool in the bone marrow with hematopoietic stem cells (HSCs) is a way to normalize its function. According to the data of several studies, HSCs transplantation as an independent option or after a course of chemotherapy allows to ensure a more pronounced clinical effect and extend its duration [7, 35].

In a clinical trial with the participation of 421 patients with AL amyloidosis, the sequential therapy of melphalan with SCT was accompanied by a complete hematological response in 48 % of cases and an improvement in the contractility of the heart in 38 % of cases, the median life expectancy of this category of subjects was significantly higher than in patients who did not undergo SCT [6]. The results of the long-term post-transplantation follow-up of 159 patients at the Mayo Clinic confirmed the survival of 29.5 % participants for 15 years or more [38]. Browning S. et al. admits that the life expectancy of 33 % of 264 treated patients exceeded 20 years with a group median of 7.2 years [4]. Nevertheless, the given data mainly refer to the patients with mild heart damage, or the start of treatment in the early stages of the disease. In general, SCT requires a careful selection of suitable candidates due to the associated toxicity. According to another research group representing the Mayo Clinic, no more than 25 % of AL amyloidosis patients meet the necessary criteria

for SCT due to high iatrogenic mortality during treatment and the absence of a significant clinical effect in the late stages of the disease [43]. In such cases, SCT can be used after heart transplantation as an effective way to prevent repeated deposition of amyloid in the myocardium [10]. In some cases, prior application of chemotherapeutic regimens allows to improve the patient's clinical condition to a sufficient extent for SCT [31].

An alternative approach to the treatment of AL amyloidosis with a cytoprotective focus on myocardial tissue is promising, but insufficiently studied. There are data on the ability of MSCs to cause the degradation of amyloid fibrils by activating the paracrine secretion of extracellular matrix proteins, growth factors and macrophage recruitment [22]. In an experimental study, Lin et al. it showed that the addition of amyloid protein to human cardiomyocytes resulted in their clustering around fibrils, severe damage to the membranes and nuclei with complete growth inhibition, but a similar effect was not observed in MSCs [25]. Moreover, the co-incubation of both cell cultures with the addition of the pathological protein was accompanied by low-expressed signs of pyknosis, preservation of growth potential, and slight apoptosis of cardiomyocytes. The authors failed to determine the complex of mechanisms involved in such an effect, however, the role in this process of reducing the level of cardiac fibrosis markers (collagen and fibronectin) was confirmed.

The involvement of fibrosis in the development of amyloid cardiomyopathy is confirmed by the data of another study, in which the addition of light chains to primary cardiac fibroblasts was accompanied by proteome remodeling, apoptosis, and activation of free-radical reactions [16]. There are also data regarding the expression by mesenchymal cells of a glycoprotein of the epidermal growth factor protein family neuregulin-1 (NRG-1) and its cardioprotective properties under conditions of oxidative stress. In an experimental study, the ability of NRG-1 to block mitochondrial pores and suppress peroxide-induced apoptosis of cardiomyocytes through PI3K-mediated way was shown [18]. Another potential mechanism of myocardial protection of MSCs in conditions of cardiac amyloidosis is their ability to modulate the immune response to pathological protein structures of amyloid fibrils [19]. Undoubtedly, the currently accumulated material on the use of cell therapy is not enough for its effective and safe introduction into clinical practice. Nevertheless, in-depth study of the mechanisms and interactions of this kind of treatment opens wide prospects for cardiac regeneration and more effective treatment of cardiac amyloidosis.

CONCLUSION

Today, stem cells play a major role in the development of regenerative medicine and have significant potential for the treatment of serious non-coronary cardiac diseases. Based on the analysis of literature data, it can be stated that today stem cell therapy, primarily of mesenchymal origin, has proven its effectiveness in DCM for improving the structural and functional state of the heart for a period of at least 12 months both in experimental models and in clinical studies. This opens up new opportunities for the treatment of patients with DCM with insufficient effectiveness of the optimal drug therapy of heart failure, and also, in certain clinical cases allows to gain time in waiting list for a heart transplantation. The possibility of using stem cell transplantation as a method of treating myocarditis has a serious theoretical basis, proven in experimental studies on laboratory animals, but requires conducting large-scale randomized clinical trials. In patients with amyloidosis, cell therapy has a systemic effect, which is manifested in the decrease of amyloid deposition and the prevention of structural and functional disorders of organs and systems, including the heart.

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Стовбурові клітини в терапії міокардиту та кардіоміопатій: перспективні напрями



Коваленко В. М., Несукай О. Г., Чернюк С. В., Козлюк А. С.

ДУ «Національний науковий центр «Інститут кардіології, клінічної та регенеративної медицини ім. акад. М. Д. Стражеска» НАМН України, Київ, Україна

РЕЗЮМЕ

Огляд літератури присвячено аналізу сучасних даних щодо ефективності трансплантації стовбурових клітин у хворих з некоронарними хворобами серця: міокардитом, дилатаційною кардіоміопатією та системним амілоїдозом з ураженням серця. Наведено результати експериментальних досліджень на лабораторних тваринах та клінічних випробувань, що стосуються застосування різних типів стовбурових клітин, їх механізмів дії та перспектив застосування при некоронарній патології серця. Зроблено акцент на необхідності проведення подальших рандомізованих багатоцентрових клінічних досліджень, особливо у хворих із запальним ураженням міокарда, із залученням великої кількості пацієнтів.

КЛЮЧОВІ СЛОВА: стовбурові клітини; клітинна терапія; дилатаційна кардіоміопатія; міокардит; амілоїдоз