

Myocarditis: expert opinions and new research opportunities

Kanorskiy S.G.¹, Mamedov M.N.²

¹ Kuban State Medical University, Krasnodar, Russia.

² National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russia.

AUTHORS:

Sergey G. Kanorskiy, MD, PhD, Professor, Head of the Therapy department, Kuban State Medical University, Krasnodar, Russia. ORCID: 0000-0003-1510-9204

Mekhman N. Mamedov, MD, PhD, Professor, Head of the Secondary Prevention of Noncommunicable Diseases Department, National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russia. ORCID: 0000-0001-7131-8049

Analysis of data from the contemporary literature confirms a number of gaps in the diagnosis and treatment of myocarditis. Sufficiently accurate data on the prevalence of myocarditis are available only for individual clinical situations, as endomyocardial biopsy and viral genome testing are rarely performed in routine clinical practice. The pathways that determine the transition from myocardial inflammation to chronic ventricular dysfunction have not been definitively established in viral infections. Therapy with immune checkpoint inhibitors in oncology, vaccination, and genetic predisposition to myocarditis are the subject of active research. Cardiovascular imaging, particularly magnetic resonance imaging, plays an important role in diagnostic and therapeutic decisions. Endomyocardial biopsy may be considered on a case-by-case basis depending on the likelihood of finding treatable disease. Current clinical guidelines for the management of patients with myocarditis, based on expert opinion alone, include treatment of heart failure, rhythm and conduction disorders. Specific therapies, particularly immunosuppression, continue to be evaluated in ran-

domized trials. Ongoing clinical trials will contribute to the development of standardized treatment regimens for patients with acute myocarditis.

Keywords: myocarditis, pathogenesis, magnetic resonance imaging, endomyocardial biopsy, heart failure, treatment, immunosuppression.

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Introduction

Myocarditis is an inflammatory disease of the myocardium that has traditionally been diagnosed based on established histologic, immunologic, and immunohistochemical criteria [1]. Since the introduction of the Dallas criteria for myocarditis, endomyocardial biopsy has been the standard method of diagnosis [2]. However, the diagnostic workup has changed over the last two decades due to the availability of new tools, mainly the determination of cardiac troponin concentration in blood by a highly sensitive method and cardiac magnetic resonance imaging (MRI) [3]. In routine clinical practice, a combination of symptoms and signs, laboratory tests and imaging studies is often sufficient to make the diagnosis of myocarditis.

In recent years, diagnostic criteria for myocarditis associated with coronavirus infection (COVID-19) or COVID-19 vaccination have been adapted from those established by the Centers for Disease Control and Prevention and the Brighton Collaboration [4, 5]. As a result, the definition and diagnostic methods for myocarditis are not uniform and can vary widely. The lack of simple and widely available diagnostic methods, as well as a universal definition of myocarditis, largely explains the lack of development of treatment options for myocarditis compared to other cardiac pathologies.

The aim of the review article is to analyze the data of modern literature on epidemiology, etiology, pathogenesis, clinical manifestations, diagnosis and treatment of myocarditis, to identify existing gaps and contradictions in scientific data, to substantiate the feasibility and methodology of further research on this topic.

Principles of literature search

In accordance with the principles of the PRISMA systematic review [6], we searched literature sources in eLIBRARY and MEDLINE/PubMed databases using the keywords "myocarditis", "epidemiology", "etiology", "pathogenesis", "clinical presentation", "COVID-19", "diagnostics", "treatment" with selection of the type of articles "Clinical Trial", "Meta-Analysis", "Randomized Controlled Trial", "Review", "Systematic Review" published for the period from January 1, 2013. to June 20, 2023 in English and Russian languages. After screening 10626 literature sources, 1771 most relevant articles available in full-text format were selected and analyzed, 59 of them were included in the article.

Etiology and pathogenesis

Myocarditis can be caused by a variety of infectious or non-infectious agents, including viruses, activation of the immune system (e.g., autoimmunity in sarcoidosis, Sjögren's disease, systemic lupus erythematosus, and vasculitis, immune stimulation by vaccination or cancer treatment), or exposure to toxins and drugs, including endogenous biochemical compounds produced in amyloidosis and thyrotoxicosis. In infectious forms of myocarditis, viruses are the most common etiologic factor. In certain populations, non-viral pathogens (e.g., bacteria *Corynebacterium diphtheriae*, *Borrelia burgdorferi*, and parasites *Trypanosoma cruzi*) and streptococcal autoimmune rheumocarditis remain significant [7].

Data on the true prevalence of viral myocarditis are not available because endomyocardial biopsy and viral genome testing are rarely performed in routine clinical practice. In addition, seasonal, geographic, and socioeconomic differences, as well as different attitudes toward vaccination, must be taken into account. Virus-mediated myocarditis can be caused by cardiotropic viruses such as adenoviruses and enteroviruses (e.g., coxsackievirus), vasculotropic viruses (e.g., parvovirus B19 — PVB19), lymphotropic viruses (e.g., cytomegalovirus, Epstein-Barr virus, and herpes virus 6 — HHV-6), cardiotoxic viruses (e.g., hepatitis C virus, human immunodeficiency virus — HIV-1), hepatitis C virus, human immunodeficiency virus, and influenza virus), and potentially cardiotoxic angiotensin-converting enzyme 2-tropic viruses (e.g., coronaviruses, including the novel SARS-CoV-2 coronavirus) [8]. The epidemiologic shift from traditional cardiotropic viruses to PVB19 and HHV-6 has been evident over the past 30 years. However, since PVB19 and HHV-6 are also found in the normal heart or in other diseases, it has been proposed to consider the cause of myocarditis as exceeding the threshold of 500 copies of viral DNA per microgram of biopsy tissue [9]. Unfortunately, in Russia there are no validated test systems designed for quantitative assessment of viral copies in myocardial biopsy specimens to evaluate viral replication.

The current understanding of the pathophysiology of viral myocarditis is mainly based on the results of experimental studies of cardiotropic viruses in mice with three phases:

- 1) viral entry into cardiomyocytes via transmembrane receptors with necrosis, apoptosis, and activation of innate immunity (1 to 7 days);

2) viral replication, activation of acquired immune responses with T-cell infiltration and autoantibodies (1 to 4 weeks);

3) viral clearance or progression to dilated cardiomyopathy (months to years) [10].

The notion that non-major cardiotropic viruses cause direct tissue damage or act as triggers of immune-mediated damage remains controversial. The latter mechanism is likely to occur in myocarditis associated with SARS-CoV-2 and other respiratory viruses [11]. However, the regulatory switch between inflammatory and reparative responses in the heart in response to viral infection is poorly understood. In addition, the pathways that determine the transition from myocardial inflammation to chronic ventricular dysfunction have not been definitively identified, i.e., it is unknown why some patients recover from myocarditis and others do not.

In the context of COVID-19, the mechanisms of cardiac damage may be multifactorial and include not only endotheilitis or myocarditis, but also myocardial damage due to mismatch between oxygen demand and supply, microvascular thrombosis, systemic hyperinflammatory response, and myocardial ischemia [12].

The use of several groups of pharmacological agents (neuroleptics, cytostatics, salicylates, immunotherapy agents, vaccines) has been recognized as a cause of myocarditis [13]. Recently, myocarditis has been proven to be a rare complication of COVID-19 vaccination when an mRNA-based vaccine is used [8]. In such cases, the vaccine is not necessarily the sole cause, and myocarditis may be caused by promotion, reactivation, or acceleration of naturally occurring myocarditis by viral or immune-mediated mechanisms [14].

Immune checkpoint inhibitor therapy is a novel treatment option for advanced cancer in which antibodies targeting cytotoxic T-lymphocyte antigen 4, cell apoptosis stimulator 1, or programmed cell death ligand 1 are used to enhance a T-cell-mediated immune response against tumor cells. However, systemic immune-mediated adverse events, including potentially life-threatening myocarditis, have been observed with increasing frequency, especially when combined with immune checkpoint inhibitors [15].

The role of genetic predisposition as a contributing factor in the development of myocarditis has now been documented, with putative pathogenic variants in genes related to cardiomyocyte structure and func-

tion occurring in up to 16 % of cases. According to the "two-hit" hypothesis, the genetic substrate may play a critical role in the phenotypic outcome in patients exposed to infectious or toxic factors. Genetic testing may be considered in all familial forms of myocarditis, not just familial cardiomyopathy [16].

The gut microbiome is a potential risk modifier for myocarditis. Mimetic peptides of commensal gut bacteria may contribute to inflammatory cardiomyopathy in genetically predisposed individuals [17].

Clinical manifestations

Myocarditis has different clinical manifestations depending on the degree of organ damage [18]. In an uncomplicated clinical picture (preserved left ventricular ejection fraction (LVEF) and absence of ventricular arrhythmias), the main symptoms of myocarditis are chest pain, dyspnea and tachycardia. New or worsening heart failure, critical hemodynamic disturbances (fulminant myocarditis with cardiogenic shock and severe LV dysfunction), and life-threatening arrhythmias or conduction disturbances (sustained ventricular arrhythmias, grade III atrioventricular block, and sudden death) may occur. Irregular, polymorphic ventricular arrhythmias are typical of active myocarditis and regular, monomorphic arrhythmias are typical of chronic myocarditis [19].

In the past, the diagnosis of myocarditis was based on the results of endomyocardial biopsy, which was mainly performed in patients with a moderate or high risk of complications. The use of new non-invasive diagnostic tools has led to the identification of a larger population of patients with clinical suspicion of myocarditis, including those with a more favorable prognosis [20].

An analysis of data from an Italian registry of acute myocarditis cases showed that most patients were without complications, but with chest pain in 97 % and ST-segment elevations on the electrocardiogram (ECG) in 62 % of cases, without death or heart transplantation at 5-year follow-up [21]. Heart transplantation or death from cardiac causes has been reported almost exclusively in patients with LVEF <50 %, sustained ventricular arrhythmias, hemodynamic instability on hospital admission, or with a combination of these manifestations. In this complicated course of myocarditis, the incidence of death or heart transplantation was 10.4 % at 30 days and 14.7 % within 5 years [21]. Analysis of data from a multicenter registry of

endomyocardial biopsies confirming acute myocarditis showed a prognostic effect of systolic dysfunction (LVEF <50 %) and hemodynamic disturbances during hospitalization on the rate of death or heart transplantation — 27.8 % within 60 days in patients with cardiogenic shock compared to 1.8 % in the absence of shock [22]. The prognostic value of histologic characterization of the inflammation with the highest risk of adverse outcome in confirmed giant cell myocarditis has been convincingly demonstrated [23]. An unfavorable effect on long-term survival after myocarditis of female gender and high myocardial antibody titer has also been reported [24].

Giant cell myocarditis should always be suspected in patients with rapidly progressing heart failure, cardiogenic shock with or without conduction disturbances, when there is no positive response to conventional therapy. The prognosis in such cases is unfavorable, with a mortality or heart transplantation rate within next 3 years of approximately 85 % [25]. However, early diagnosis, rapid initiation of aggressive immunosuppressive therapy and/or mechanical hemodynamic support can reduce the risk of death or the need for heart transplantation [26].

The rates of mortality or heart transplantation in patients with fulminant eosinophilic myocarditis is more than 1/4 of cases at 60 days of follow-up [23]. The use of glucocorticoids in this setting has been shown to reduce in-hospital mortality, but the data supporting this treatment option and the randomized trials themselves are still insufficient [27].

Patients with cardiac sarcoidosis may have conduction abnormalities and heart failure. Such patients are at risk of sudden death and may require an implantable cardioverter-defibrillator [28].

Myocarditis associated with COVID-19

Myocarditis is thought to be relatively rare in COVID-19, but in nearly 40 % of cases where it is considered a definite or probable diagnosis, the disease has a fulminant course [11]. Hemodynamic instability, the need for temporary mechanical circulatory support, and a fatal outcome are more likely in patients with concomitant pneumonia than in those without [29]. Patients with COVID-19 have a more than 5-fold increased risk of myocarditis within one year of infection [30].

Apparently, SARS-CoV-2 is one of the etiologic factors of both acute myocarditis in the initial (actually

infectious) phase of the disease and subacute (within 1 to 3 months), as well as of the chronic post-infection myocarditis, caused not only by viral persistence in the myocardium up to 9 months, but primarily by severe autoimmune reactions, which requires determination of the indications for immunosuppressive therapy, its extent and duration [31].

Myocarditis associated with COVID-19 vaccines

The analysis of retrospective data from large populations showed that myocarditis following administration of the mRNA vaccine BNT162b2 (Pfizer-BioNTech) was very rare, most commonly in males aged 16–29 years (10.7 cases per 100,000), occurring 1–7 days after the second dose and usually resolving spontaneously within a few days [32]. An increased risk of myocarditis after COVID-19 vaccination with mRNA vaccines (e.g., BNT162b2 or mRNA-1273 [Moderna]) has also been reported in adolescent boys and young men after the second dose. In 87 % of cases, myocarditis symptoms resolved by hospital discharge [33].

Immune Checkpoint Inhibitors-Related Myocarditis

Analysis of follow-up data from the largest series of patients with myocarditis associated with immune checkpoint inhibitor therapy in oncology practice showed early onset of symptoms (median time interval after initiation of therapy was 34 days) and high mortality (50 % of cases) [34]. The growing understanding of the severity of this complication, as well as the increasing number of patients receiving combination therapy with immune checkpoint inhibitors, has led to recommendations to record ECGs and determine troponin levels initially and weekly during the first six weeks of treatment, although there is still no convincing evidence of the efficacy and value of such monitoring [35].

Diagnostic instruments

Given the non-specific and variable clinical presentation of patients with myocarditis, cardiovascular imaging plays an important role in diagnostic and therapeutic decisions. According to the European Society of Cardiology (ESC) Working Group [36], non-invasive diagnostic tests help to establish the diagnosis of “suspected myocarditis” in the presence of clinical manifestations and criteria in four categories:

- 1) laboratory tests;
- 2) electrocardiography, Holter ECG monitoring and exercise testing;
- 3) functional and structural assessment of the heart with imaging studies (echocardiography, angiography, MRI);
- 4) detailed tissue characterization with cardiac MRI.

Standard transthoracic echocardiography serves as the initial cardiac imaging modality and plays a role in assessing the likelihood of myocarditis because of its availability and ability to be used as a bedside technique in the acute care setting. However, echocardiography is not sensitive enough to detect inflammation in the absence of wall motion abnormalities not due to acute ischemia, which limits its clinical utility. This imaging modality can be used to dynamically monitor structural and functional changes in the heart. Speckle-tracking echocardiography allows the assessment of global longitudinal and radial myocardial deformation, more accurately diagnosing LV dysfunction, but has limited application due to high cost.

The ESC experts recommended selective coronary angiography and endomyocardial biopsy for all patients meeting the diagnostic criteria for clinically suspected myocarditis [36]. More recently, a risk-based approach to diagnostic testing and emergency management of clinically suspected myocarditis has been proposed by expert consensus [37]. It is suggested that endomyocardial biopsy should be performed in patients with clinical suspicion of myocarditis and the following features:

- 1) Cardiogenic shock or acute heart failure requiring inotropic or mechanical circulatory support; ventricular arrhythmias or Mobitz grade II or III atrioventricular block, especially with recent onset of symptoms, with or without moderate LV dilatation, peripheral blood eosinophilia, or associated systemic inflammatory disease;
- 2) Persistent or recurrent release of necrosis markers, especially in the setting of probable autoimmune disease or ventricular arrhythmias and high-degree atrioventricular block;
- 3) Heart failure in patients receiving therapy with immune checkpoint inhibitors.

In other clinical situations, cardiac MRI should be considered as an initial diagnostic test to detect inflammation, and endomyocardial biopsy may be considered on a case-by-case basis depending on the likelihood of detecting a treatable condition [37].

According to authoritative domestic researchers, if biopsy cannot be performed, complex non-invasive diagnostics allows to diagnose myocarditis of severe and moderate course with different degrees of probability, as well as to perform effective immunosuppressive therapy, the refusal of which is not justified in many cases [38].

Cardiac MRI

In case of clinical suspicion of myocarditis, cardiac MRI is a valuable diagnostic tool and has the highest sensitivity when performed within 2-3 weeks of the onset of clinical manifestations. Cardiac MRI is also useful for dynamic follow-up of disease progression after 6-12 months. The MRI markers for the diagnosis of myocarditis proposed in 2009 (Lake Louise Criteria) were updated in 2018 to include T2-mapping techniques, increasing their sensitivity and specificity for detecting active inflammation to 88 % and 96 %, respectively [39].

Exclusion of pathology on MRI in a patient with clinical suspicion of myocarditis is associated with a good prognosis. In contrast, late gadolinium enhancement in the middle layer of the interventricular septum and low LVEF are recognized as strong predictors of an unfavorable outcome. Late gadolinium enhancement and disappearance of edema on dynamic imaging are negative predictors compared to not only complete resolution of the pathological process, but also simultaneous preservation of late gadolinium enhancement and edema, as the latter data indicate preservation of process activity with potential for recovery [40].

Endomyocardial biopsy

Myocarditis is diagnosed when histologic examination of at least three 1–2 mm tissue samples obtained by endomyocardial biopsy reveals an inflammatory infiltrate with necrosis or degeneration of adjacent myocytes. Subtypes such as lymphocytic, eosinophilic, giant cell myocarditis and cardiac sarcoidosis can be identified, each with specific prognostic and therapeutic implications [41].

Quantitative criteria for inflammation were specified in the 2013 ESC guidelines [36], but they have not been validated in a population of non-European origin. The diagnostic utility of endomyocardial biopsy is maximized when performed within 2 weeks of symptom onset. Its sensitivity can be improved by in-

creasing the number of biopsy specimens and by performing endomyocardial biopsy under imaging guidance or electroanatomic mapping [41]. The availability of immunohistochemical staining to characterize inflammatory cells leads to an increase in positive endomyocardial biopsy results.

In addition to histological and immunohistochemical evaluation of biopsy specimens, polymerase chain reaction or in situ hybridization analysis is recommended to detect the presence of viruses, although the causal relationship between viral infection and cardiac injury is still being studied. Standardization of methods for identification and quantification of the viral genome is needed [7]. Meanwhile, the presence of viral genome in the absence of inflammatory cells is not a criterion for the diagnosis of myocarditis.

Other tests

In routine practice, markers of myocyte inflammation such as erythrocyte sedimentation rate and C-reactive protein levels are commonly evaluated, although they are not specific and are not necessarily elevated in myocarditis [18, 36]. Cardiac troponin is a more sensitive marker than creatine kinase and its MB fraction [36]. Russian experts recommend the study of troponins I, T levels in the blood of all patients with myocarditis as part of the initial examination and in the course of dynamic follow-up [42]. Determination of troponin levels by a highly sensitive method is a valuable tool that helps to identify myocarditis more accurately than the conventional troponin test. Russian experts also recommend testing the level of natriuretic peptides, such as the N-terminal precursor of brain natriuretic peptide, in the blood of all patients with myocarditis as part of the initial examination and during dynamic follow-up [42]. However, changes in this parameter are not specific for myocarditis, and normal levels do not exclude myocarditis [36].

The recommendation to determine the level of serum cardiac autoantibodies specific for myocardial tissue in all patients with myocarditis [42] is unfortunately not feasible due to the lack of standardized kits for such a study in the Russian Federation.

MicroRNA profiling in blood and endomyocardial biopsy samples in search of disease biomarkers at the whole transcriptome level has been studied with encouraging results, but there was no correlation between tissue and blood marker levels [43].

It has been shown that circulating RNA synthesized by type 17 helper T cells (hsa-miR-Chr8:96) can be used to differentiate patients with myocarditis from those with myocardial infarction [44].

Treatment

No large-scale prospective controlled trials have been conducted to assess the efficacy of myocarditis treatment and its impact on prognosis. Existing guidelines are based only on expert opinion [36, 42]. Therefore, myocarditis therapy includes urgent correction of life-threatening conditions (refractory circulatory failure, cardiac rhythm and conduction disturbances), treatment of chronic heart failure according to current recommendations [28, 45, 46], and, if possible, specific etiopathogenetic intervention on viral infection and immune inflammation [18, 42].

Conventional therapy

Patients with heart failure who remain hemodynamically stable should be treated with diuretics, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and beta-adrenergic blockers. Additional treatment with mineralocorticoid receptor antagonists should be considered in patients with persistent heart failure despite adequate therapy. Whether early treatment of patients with preserved LVEF to reduce myocardial inflammation, remodeling and scarring is appropriate remains unclear.

Patients with heart failure and hemodynamic instability require the use of inotropic agents. Their care should be managed in the intensive care unit with the possibility of respiratory and mechanical cardiopulmonary support; referral of such patients to a specialized cardiac center should be considered. In patients with cardiogenic shock, severe ventricular dysfunction refractory to drug therapy, mechanical circulatory support with a mechanical assist device or extracorporeal membrane oxygenation (ECMO) may be required [47].

The main goals of treating severe myocarditis are to achieve hemodynamic ventricular unloading, adequate systemic and coronary perfusion, and relief of venous congestion to prevent multiorgan dysfunction and allow recovery, heart transplantation, or the use of an implantable circulatory support device. Temporary use of intra-aortic balloon counterpulsation, veno-arterial ECMO, centrifugal pump, and axial-rotary pump should be considered.

The use of devices that reduce LV afterload, such as extracorporeal left ventricular bypass or intra-aortic left ventricular bypass with an axial pump, alone or in combination with ECMO, is more likely to promote myocardial recovery than ECMO alone [48]. In recent years, LV unloading with a percutaneously placed axial pump (Impella; Abiomed) has been used as a treatment option in patients with cardiogenic shock, either as sole LV support with preserved right ventricular function or in combination with extracorporeal hemodynamic support or with right-sided placement of such a pump. If the patient cannot be withdrawn from mechanical circulatory support after 2–3 weeks, the implantation of a mechanical LV support device or heart transplantation should be considered [18].

There are no specific guidelines for the management of rhythm and conduction disturbances in patients with myocarditis. After the acute phase of the disease, treatment should be in accordance with current recommendations for the management of patients with arrhythmias and the use of electronic cardiac devices [45, 46]. Because myocarditis is a potentially reversible condition, a step-by-step approach to therapy during the acute phase is suggested. In cases of complete atrioventricular block, electrocardiostimulation may be required. The use of an implantable cardioverter-defibrillator should be delayed until after the acute phase of myocarditis, usually within 3–6 months of onset; if necessary, the use of a portable cardioverter-defibrillator may be considered.

In competitive athletes, physical activity should be restricted during the acute phase of myocarditis and for a period of 3 to 6 months thereafter, depending on the clinical severity and duration of the acute phase of the disease [49]. After resolution of myocarditis, reassessment of clinical status is indicated prior to resumption of competitive sports participation. Survivors of myocarditis should be followed every 6 months [36, 42].

Specific therapy

After eliminating the causes of eosinophilia, such as the effects of drugs or parasites, the main therapy for eosinophilic giant cell myocarditis and cardiac sarcoidosis is the administration of immunosuppressants (glucocorticoids alone or together with azathioprine and/or cyclosporine) [50, 51]. There is no specific therapy for acute lymphocytic myocarditis, ex-

cept for forms associated with systemic disease and therapy with immune checkpoint inhibitors [36, 52].

Although there is a rationale for immunosuppressive therapy in the acute phase of myocarditis in patients at high risk of adverse outcomes, there are no data from large prospective multicenter trials focused on this issue. In a few small single-center studies in patients with virus-negative chronic inflammatory cardiomyopathy confirmed by endomyocardial biopsy, treatment with prednisolone and azathioprine showed favorable results, including a significant increase in LVEF [53]. The authors of the first of these studies recently reported long-term (up to 20 years) clinical outcomes in 85 patients originally enrolled in the TIMIC trial (group A), compared with outcomes in the control group of patients matched by pseudorandomization (statistical technique of propensity score matching) and not treated according to the TIMIC protocol (group B). In group A, immunosuppressive therapy reduced the risk of a combination of adverse outcomes (cardiovascular death, heart transplantation) by 6.77 times with the background of persistent improvement of LVEF compared with group B, in which implantation of a cardioverter-defibrillator was also performed more frequently [54]. The potential efficacy of an inexpensive and sufficiently safe immunosuppressive therapy in targeted use after assessment of morphomolecular characterization of myocardial tissue should be confirmed or refuted in a multicenter, randomized, double-blind, placebo-controlled trial.

Current European and Russian guidelines do not recommend the widespread use of immunosuppressive therapy in patients with myocarditis; non-steroidal anti-inflammatory drugs (in the absence of pericarditis), glucocorticoids also are not indicated (except for autoimmune, eosinophilic, granulomatous and giant cell acute myocarditis). For the safe use of immunosuppressive therapy, histochemical analysis of the viral genome from endomyocardial biopsy specimens is recommended to confirm active viral-negative myocarditis [36, 42]. The American Heart Association document on the management of fulminant myocarditis [55] recommends immediate intravenous administration of 1 g of methylprednisolone, even before endomyocardial biopsy or other investigations are performed, if there is reasonable suspicion of an immune-mediated form of myocarditis. If the diagnosis of giant cell myocarditis is confirmed,

immunosuppressive agents should be added to the treatment regimen.

Recently, empiric treatment with intravenous glucocorticoids has been proposed for patients with cardiogenic shock or acute myocarditis complicated by heart failure, ventricular arrhythmias, or high-degree atrioventricular block [18]. Supportive glucocorticoid therapy is appropriate in patients with eosinophilic or giant cell myocarditis, cardiac sarcoidosis, or confirmed autoimmune disease. In rare cases where enterovirus, cytomegalovirus, or adenovirus are detected, immunosuppressive therapy may be canceled [56]. In patients who test positive for PVB19 or HHV-6, maintenance of immunosuppression depends on the initial response to therapy and viral load [9, 18].

Alternative treatments for specific conditions in patients with virus-negative or autoimmune inflammatory cardiomyopathy include removal of autoantibodies (immunoadsorption) followed by intravenous immunoglobulin therapy [57]. This treatment is currently being evaluated in a large multicenter trial in patients with dilated cardiomyopathy. Intravenous immunoglobulin therapy is widely used in pediatrics, but the use of such treatment in adults with lymphocytic myocarditis is limited.

There are insufficient data to support antiviral therapy for acute myocarditis. Beneficial effects of interferon treatment with virus elimination and the improvement of the functional class of heart failure according to the New York Heart Association classification have been demonstrated only in chronic inflammatory cardiomyopathy caused by adenovirus, enterovirus, and PVB19 confirmed by endomyocardial biopsy [7]. Treatment with anti-herpes viral drugs may be considered in patients with Epstein-Barr virus, cytomegalovirus, or HHV-6 infection [58]. Whether a combination of antiviral and immunosuppressive therapy can be used in some patients with virus-positive inflammatory cardiomyopathy at a certain stage of the disease remains to be studied.

Ongoing clinical trials are evaluating the role of high-dose methylprednisolone (The Myocarditis Therapy with Steroids trial — MYTHS); the interleukin-1 receptor antagonist anakinra (The Anakinra versus Placebo for the Treatment of Acute Myocarditis — ARAMIS) in patients with acute myocarditis complicated by heart failure or cardiogenic shock, while excluding patients with hemodynamic instability; and

abatacept (a protein that selectively modulates the key co-stimulatory signal required for full activation of T lymphocytes) for the treatment of myocarditis associated with immune checkpoint inhibitor therapy (Abatacept for the Treatment of Immune-Checkpoint Inhibitors Induced Myocarditis (ACHLYS)) [59].

Conclusion

Myocarditis remains an understudied pathology compared to other common diseases of the cardiovascular system. The variety of clinical manifestations of myocarditis, different criteria of its histological and imaging diagnostics make it difficult to determine useful therapeutic interventions.

Studies to identify the factors that determine the progression of acute viral myocarditis to autoimmune cardiomyopathy are now urgently needed. Standardization and integration of endomyocardial biopsy, imaging, laboratory and clinical criteria are needed to better understand the phenotype of myocarditis and optimize the management of patients. New diagnostic tools, including single cell sequencing, coupled with in-depth clinical phenotyping, are needed to identify novel targets potentially amenable to therapeutic intervention. Prospective multicenter studies of the role of genetics in susceptibility to myocarditis are needed to determine its impact on disease severity and long-term outcomes.

Determination of the indications for immunosuppressive therapy for post-void myocarditis, its amount and duration is required. Understanding the pathogenesis of mRNA vaccine-induced myocarditis is important for public health. A better understanding of the cardiac damage associated with immune checkpoint inhibitor therapy in oncology, determination of susceptibility to such myocarditis, and identification of biomarkers for its early diagnosis should be researchers' priority.

Clinical trials of treatment options for myocarditis that combine knowledge of genetics, single-cell tissue analysis and cardiac imaging with patient phenotyping are needed to develop standard regimens for the treatment of patients with acute myocarditis and to ensure that the burden of myocarditis on society is reduced.

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