Diagnosis and Treatment of Myocarditis: The Role of Endomyocardial Biopsy

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Opinion statement

Viral infections often affect the heart. In the majority of cases, the course of the disease is benign and patients recover spontaneously. However, viral infection may persist and lead to acute cardiac failure or progress to dilated cardiomyopathy. Viral infections are considered to be the most common causes of myocarditis. There is evidence that intramyocardial viral persistence is associated with progressive ventricular dysfunction, even when the infiltrate is sparse or missing. The diagnosis of viral myocarditis necessitates the detection of viral genome by molecular biology techniques and the evaluation of myocardial inflammation by the immunohistochemistry on endomyocardial biopsy samples. Autoreactive myocarditis can also only be diagnosed by endomyocardial biopsy. Infiltration of leukocytes and a negative polymerase chain reaction on microbial agents are their hallmarks. Apart from symptomatic or supportive therapy, etiologic treatment strategies have to address the underlying causative virus or the autoimmune process. In symptomatic or deteriorating patients, targeted antiviral therapy is a reasonable algorithm to eradicate the virus, which will contribute to resolving inflammation or apoptosis, thus confining myocardial damage. The Marburg registry favors intravenous immunoglobulin treatment in biopsy-proven adenovirus and parvovirus B19 myocarditis combined with optimal conventional therapy to achieve virus clearance. In fulminant myocarditis, biopsy is mandatory to identify giant cell myocarditis and cardiac sarcoidosis to be treated by immunosuppression. In cardiogenic shock, the use of mechanical circulatory support by means of a ventricular assist device as a bridge to recovery may be a lifesaving approach. In perimyocarditis with dominant pericardial affection, colchicine over a period of 1 to 6 months can dissolve the pericardial effusion effectively in more than 80% of cases.

Introduction

Minor involvement of the heart in viral infections is relatively common. Many such cases are asymptomatic and resolve spontaneously. However, viral infections of the heart can also cause substantial myocardial damage leading to acute heart failure or progressively evolve to dilated cardiomyopathy and chronic heart failure. Myocarditis ascertained by endomyocardial biopsy in a dilated heart has been termed by the World Health Organization (WHO)/International Society and Federation of Cardiology (ISFC) in 1996 as dilated cardiomyopathy with inflammation. Viral cardiomyopathy has been defined as viral persistence in a dilated heart without myocardial inflammation. The World Heart Federation (WHF) Task Force defines inflammatory viral cardiomy-

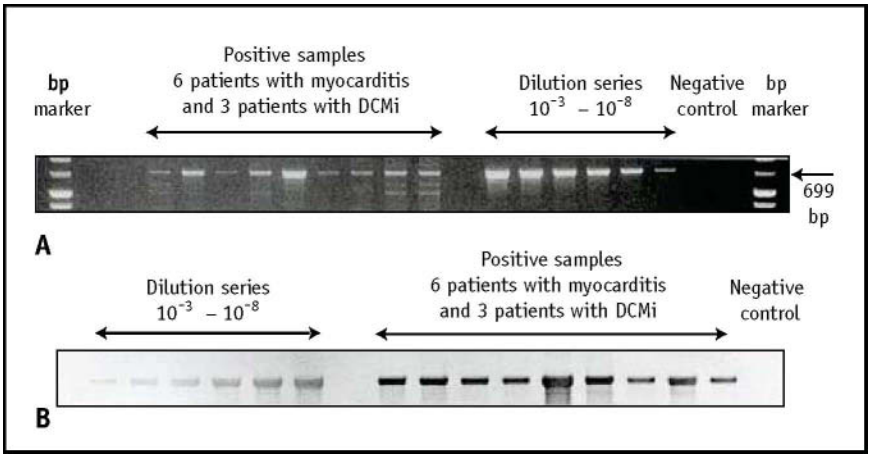

Figure 1. A, Positive polymerase chain reaction with primer pairs specific for viral protein 1 of parvovirus B19 (PBV 19). **B,** Positive Southern blot hybridization for PBV 19. bp—base pair; DCMi—dilated cardiomyopathy with inflammation.

opathy or viral myocarditis as the presence of a virus and myocardial inflammation [1,2].

Viruses most commonly associated with viral myocarditis are parvovirus B19, enteroviruses, and adenoviruses [3–6]. The spectrum of the causative viral agents depends on the focal endemic situation in a certain geographical region, the age of the patient, the application of different therapeutic procedures, and additional diseases. In most of Europe these days, parvovirus B19 is the most often identified etiologic agent of viral myocarditis (Fig. 1). In general, viruses are considered to be the most common causes of myocarditis in Europe and North America together with an autoimmune process. Several studies have demonstrated the persistence of inflammation in the heart muscle and probably also of the virus, which is associated with progressive left ventricular dysfunction and a poor prognosis [7,8•,9••].

In the pathogenesis of viral myocarditis, at least three phases can be identified; these phases may evolve from one to another, but may also overlap or be found simultaneously in the same patient. The first phase is dominated by the viral infection and replication, which causes the initial myocardial injury. Often, complete recovery or healing on a defect status is observed. Healing depends on an effective immune response and the absence of subsequent autoimmunity. However, if the immune response continues and autoimmune reactions arise despite the elimination of the virus, the second phase of the disease develops. However, autoimmunity can also occur in systemic rheumatic disorders or after myodestruction by toxic substances (drugs, alcohol), in postcardiotomy or postinfarction syndrome, or after bacterial infection (*Borrelia burgdorferi*). In this phase, additional myocardial injury occurs. In the third phase, viral infection and autoimmune reactions are decremented and the end-stage clinical picture of the idiopathic dilated cardiomyopathy dominates [10–12]. Precise knowledge of the phase in which the myocarditis has evolved is essential for the correct management of the disease and can be accomplished only by endomyocardial biopsy.

INDICATIONS FOR HOSPITALIZATION AND ENDOMYOCARDIAL BIOPSY

Hospitalization is warranted for any patients with suspected myocarditis to assess the myocardial dysfunction, observe the clinical course, and determine the etiology of the disease. Patients with acute and life-threatening deterioration of hemodynamics or severe dysrhythmias should be transferred to an intensive care unit to receive medical and mechanical circulatory support. Forms of fulminant myocarditis (giant cell myocarditis, acute lymphocytic myocarditis, or cardiac sarcoidosis) and a possible viral etiology in inflammation have to be identified early by endomyocardial biopsy.

DIAGNOSIS OF VIRAL MYOCARDITIS

Early and definite diagnosis of viral myocarditis or protracted chronic courses depends on the identification of the infective agent by molecular techniques such as polymerase chain reaction (PCR) and the detection of inflammatory infiltrates according to the WHO/ISFC [1], Dallas criteria [13], and the WHF classification [2] in the endomyocardial biopsies. Not all noninvasive approaches are capable of identifying the causative virus.

The clinical phenotype is most often dilated cardiomyopathy. It can also be a near-normal heart function and rarely hypertrophic cardiomyopathy. Studies by Matsumori et al. [14–16] suggest that hepatitis C virus is involved in the development of hypertrophic cardiomyopathy; according to the Marburg registry, parvovirus B19 and Epstein-Barr virus are also involved. Viral inflammatory cardiomyopathy may present as fulminant, acute (nonfulminant), or chronic myocarditis. Antecedent viral illness may be observed in up to two thirds of patients with myocarditis. Fulminant myocarditis is characterized by a rapid, severe, and often life-threatening deterioration of hemodynamics requiring high-dose vasopressor and/or mechanical circulatory support. Echocardiography displays severe left ventricular dysfunction, with or without ventricular dilatation. The critical and severe manifestations at presentation may, if untreated in giant

cell myocarditis or heart sarcoidosis, lead to immediate death. Spontaneous healing is also observed in patients with lymphocytic myocarditis. Acute myocarditis exhibits initially less critical symptoms and signs, but often evolves into a debilitating illness with a chronic progressive course leading to dilated cardiomyopathy. Chronic myocarditis may cause signs and symptoms of congestive heart failure only.

Rhythm disturbances, manifested as syncope, palpitations, conduction abnormalities, or sudden death, may also be observed in every stage of the disease. Ventricular arrhythmias are particularly worrisome because they are often a precursor of sudden cardiac death. In fact, myocarditis represents the major cause of sudden unexpected death in active, otherwise healthy young adults less than 40 years of age [17]. Rarely, but of most clinical interest, viral myocarditis can masquerade as an acute coronary syndrome. Angina pectoris, elevation of troponin and creatinine kinase levels, and electrocardiogram (ECG) findings such as those in myocardial infarction are present, but subsequent coronary angiography shows normal coronary arteries [6,18]. The diagnosis of myocarditis should be especially considered in younger adults presenting with the clinical picture of an acute coronary syndrome with low risk for coronary artery disease, ECG findings extending beyond the territory of a single coronary artery, antecedent flu-like symptoms, and globular rather than segmental myocardial wall motion abnormalities on echocardiography. Angina-like symptoms can also occur in accompanying perimyocarditis or by microangiopathy (parvovirus B19). The wide spectrum of the clinical manifestations of viral myocarditis depends on the underlying virus type and the age, gender, and immunocompetence of the patient.

Among laboratory results, elevated levels of troponin and creatine kinase are detected only in a small proportion of patients with myocarditis [19], mostly in fulminant and acute forms. ECG changes and rhythm disturbances are common [20,21]. Echocardiography is indispensable for the initial assessment. It may display global or regional systolic dysfunction, ventricular dilatation, right ventricular dysfunction, and/or pericardial effusion. Contrast-enhanced MRI is useful to assess myocardial inflammation [22]. Cardiac MRI may be helpful in detecting the region of myocardial inflammation, thus facilitating targeted endomyocardial biopsy of the inflammation site.

Endomyocardial biopsy remains the gold standard for the definite diagnosis of viral and autoreactive myocarditis. Endomyocardial biopsy has become a unique method for assessing myocardial inflammation and identifying the infective agent with the application of modern immunohistochemical and molecular biology investigations. PCR analysis of endomyocardial tissue identifies the infective agent with a high specificity and sensitivity and should include the following cardiotropic viruses: parvovirus B19, enterovirus, adenovirus, Epstein-Barr virus, cytomegalovirus (CMV), human herpesvirus 6, influenza viruses A and B, HIV, and hepatitis C virus. Bacterial genomes to be analyzed include *B. burgdorferi* and *Chlamydia pneumoniae*. Due to the focal nature of the inflammatory infiltrates and involvement of regions inaccessible to the bioptome, endomyocardial biopsy results may be false negative in patients with myocarditis. The size and number of the biopsy specimens directly influence the sensitivity of endomyocardial biopsy. In our institution, three biopsy samples are examined for inflammatory infiltrates by three independent pathologists, resulting in a sensitivity of up to 60%. PCR investigation of the biopsy tissue for viral genome reaches a sensitivity of 95%. Figures 2 and 3 show the clinical pathway for the diagnosis and treatment of fulminant, acute, and chronic myocarditis followed by our institution [9••].

EVALUATION OF ENDOMYOCARDIAL BIOPSY FINDINGS

Histopathologic diagnosis of myocardial inflammation has traditionally been based on the Dallas criteria [13]. According to the Dallas criteria, a focal inflammatory infiltrate (more than three infiltrating cells together) is distinguished from a diffuse inflammatory infiltration of the myocardium. In 1999, the WHF expanded the conventional histologic criteria by quantitating the inflammatory infiltrate by immunohistochemical methods. The committee chose a minimum of 14 infiltrating lymphocytes and macrophages for the definition of myocarditis [1]. The following terminology was adopted:

First biopsy

1) Acute (active) myocarditis: an infiltrate of greater than or equal to 14 leukocytes/mm^2, preferably activated T cells. The amount of the infiltrate should be quantitated by immunohistochemistry. Necrosis and degeneration are obligatory. Fibrosis may be absent or present and should be graded. 2) Chronic myocarditis: an infiltrate of greater than or equal to 14 leukocytes/mm^2, preferably activated T cells, quantitated by immunohistochemistry. Necrosis or degeneration are usually not evident, and fibrosis may be absent or present. 3) No myocarditis: no infiltrating cells or less than or equal to 14 leukocytes/mm^2.

Subsequent biopsies

4) Persistent myocarditis: criteria as in 1 or 2 above. 5) Resolving (healing) myocarditis: criteria as in 1 or 2, but the immunologic findings are sparser than in the first biopsy. 6) Resolved (healed) myocarditis: criteria corresponding to the Dallas classification. In addition, standards for the identification of the pathogenic agent by PCR were established.

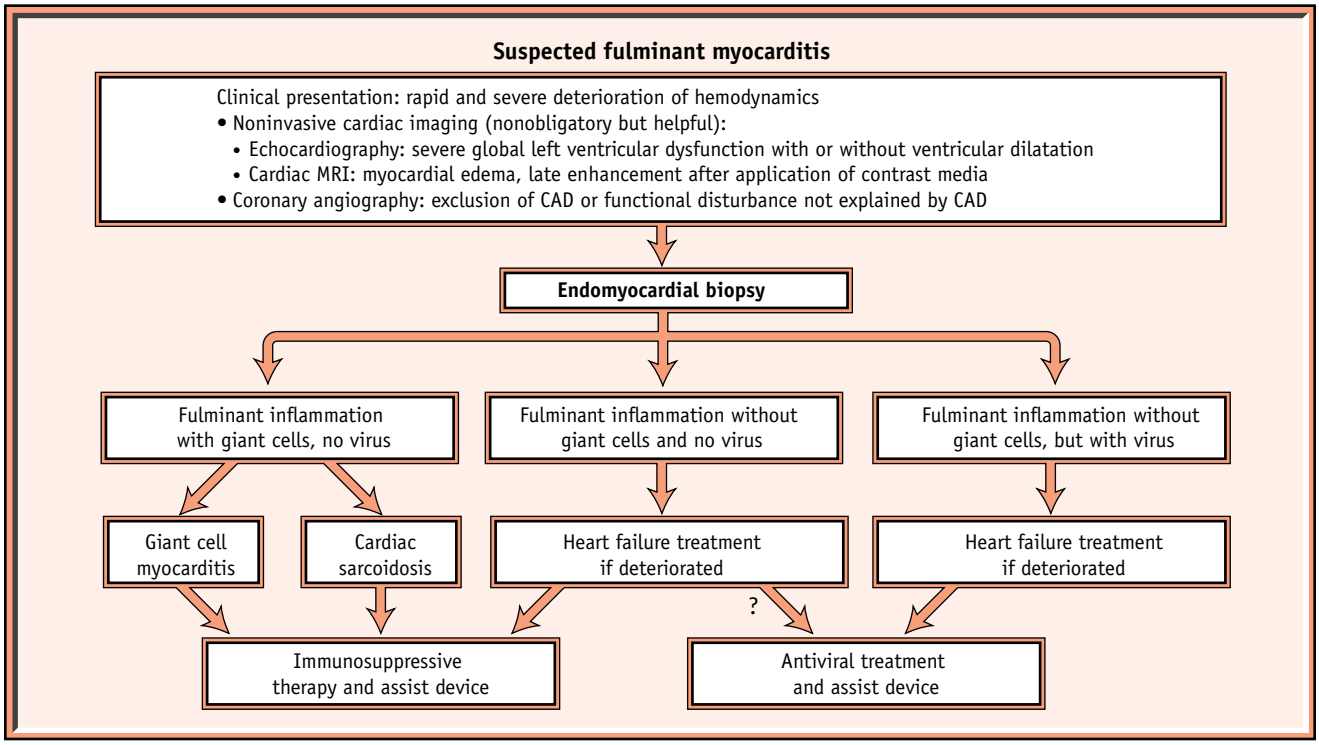

Figure 2. Pathway for the diagnosis and treatment of fulminant myocarditis. CAD—coronary artery disease. (*Adapted from* Maisch et al. [9••]; with permission.)

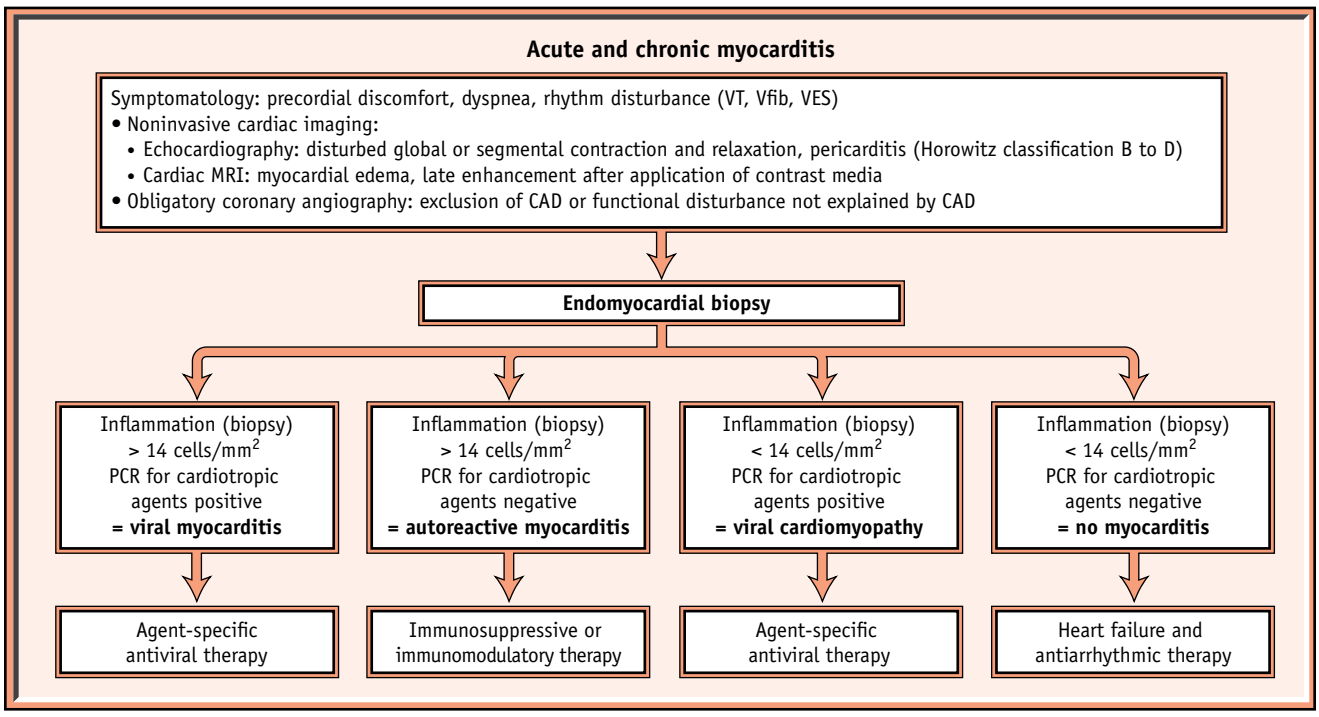

Figure 3. Pathway for the diagnosis and treatment of acute and chronic myocarditis. CAD—coronary artery disease; PCR—polymerase chain reaction; VES—ventricular extrasystole; Vfib—ventricular fibrillation; VT—ventricular tachycardia. (*Adapted from* Maisch et al. [9••]; with permission.)

Treatment

Diet and lifestyle

- Restriction of physical activity during the inflammatory phase is recommended because in experimental animal models, exercise enhanced cardiac dilatation, myocardial injury, and the inflammatory infiltrate [23,24].

Pharmacologic treatment

- In patients presenting with congestive heart failure or asymptomatic left ventricular systolic dysfunction, treatment should follow the current American College of Cardiology (ACC)/American Heart Association (AHA) recommendations: a β-adrenergic blocker, an angiotensin-converting enzyme inhibitor, a diuretic (if needed), and an aldosterone antagonist in patients with persistent New York Heart Association III to IV functional class.
- Patients presenting with fulminant myocarditis require an aggressive and intensive management of the cardiogenic shock, including positive inotropes, vasopressors, and mechanical ventricular support (intra-aortic balloon pump, ventricular assist device) in refractory cardiogenic shock. Intensive pharmacologic and mechanical hemodynamic support allow sufficient time for recovery of ventricular dysfunction. After hemodynamic stabilization, the patients should also be treated according to the ACC/AHA recommendations for the management of left ventricular dysfunction as mentioned above. Giant cell myocarditis and cardiac sarcoidosis should be treated by immunosuppression, the latter with corticosteroid alone. These two diagnoses can be made and followed up only by endomyocardial biopsy.
- Ventricular arrhythmias are common in active myocarditis, but specific antiarrhythmic treatment is indicated only in severe refractory ventricular arrhythmias. Implantation of a cardioverter-defibrillator should be considered when all other means of controlling ventricular arrhythmias are unsuccessful. However, because spontaneous or treatment-derived remission may occur, the implantation of a cardioverter-defibrillator should be deferred, whenever possible, to allow sufficient time for recovery of ventricular function. Patients with complete heart block may require implantation of a temporary pacemaker. The atrioventricular block is usually transient, and insertion of a permanent pacemaker is rarely indicated.
- The treatment aims in viral myocarditis are the elimination of the inflammatory cells from the myocardium and the eradication of the causative virus. Accordingly, causative treatment regimens with antiviral and immunosuppressive agents have been applied from various investigators. Their effect has to be evaluated by hemodynamic improvement and the eradication of inflammation and the virus in subsequent biopsy samples.

Antiviral therapy

- Because viral persistence in the myocardium is associated with progressive cardiac dysfunction [7,8•], antiviral therapy has become a logical approach. Conventional treatment of the ventricular dysfunction does not address the underlying causative agent and may delay but not prevent the progression of the disease.

Intravenous immunoglobulins

- Intravenous immunoglobulins have been used for the treatment of viral inflammatory cardiomyopathy and myocarditis in general due to their antiviral and anti-inflammatory effects. The treatment with intravenous immunoglobulins demonstrated beneficial results in several case reports [25–27] and uncontrolled trials [28,29] with considerable improvements of cardiac function and ejection fraction. The only randomized placebo-controlled trial evaluating intravenous immunoglobulins showed no difference in event-free survival or in improvement of left ventricular dysfunction [30]. However, only 10 patients of the enrolled 62 patients demonstrated a cellular infiltrate compatible with active myocarditis according to the Dallas criteria. Moreover, a distinction between viral and nonviral (autoreactive) myocarditis was not made. Thus, histologic entrance criteria varied considerably and, most important, etiopathogenesis was unclear.
- Derived from our own data, hyperimmunoglobin demonstrated the eradication of inflammation and virus in biopsy-proven CMV myocarditis [31•].
- Treatment of parvovirus B19–associated myocarditis remains complicated. We treat these patients with intravenous immunoglobulins, according to our open-label parvovirus B19 registry study. The immunoglobulins can eradicate the myocardial inflammation in almost all cases, leading to clinical improvement, but the parvovirus cannot be eliminated completely in up to one half of the patients.
- The clinical value of antiviral treatment is being assessed in the double-blind, randomized, placebo-controlled ESETCID (European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases) in our center [32,33]. In the ESETCID, patients with left ventricular ejection fraction less than or equal to 45%, biopsy-proven myocarditis according to the WHO/WHF criteria, and PCR positivity for enterovirus are randomly assigned to treatment with interferon (IFN)-α or placebo; adenovirus- or parvovirus-positive patients are randomized to immunoglobulins or placebo; and CMV-positive patients are randomized to hyperimmunoglobulins and placebo. The results of this study will add new important information on antiviral treatment in viral myocarditis.

Immunoglobulin in parvovirus B19 myocarditis

Standard dosage	10 to 20 g of immunoglobulin (Pentaglobin; Biotest-Pharma Gmbh, Dreieich, Germany) are given intravenously at day 1 and day 3.
Contraindications	The drug is contraindicated in patients with known anaphylactic or severe systemic response to immunoglobulin.
Main drug interactions	The product may interfere with the response to live viral vaccines such as measles, mumps, and rubella.
Main side effects	Because they are made of human blood, immunoglobulins may carry a risk of transmitting infectious agents and, theoretically, the Creutzfeldt-Jakob agent. Other adverse effects include allergic reactions, fever, nausea and vomiting, headache, and back pain. Rare side effects that have been reported are an aseptic meningitis syndrome, hemolysis, thrombotic events, and the transfusion-related acute lung injury. Our own observation of more than 250 patients shows that this is a well-tolerated therapy.
Cost/cost-effectiveness	Relatively expensive: 100 mL of the product containing 5 g of immunoglobulins costs 426.10 euros.

Hyperimmunoglobulin in CMV myocarditis

Standard dosage	Hyperimmunoglobulin (Cytotect; Biotest-Pharma Gmbh) 4 mL/kg of body weight one time per day on days 0, 4, and 8, then 2 mL/kg of body weight on days 12 and 16.
Contraindications	The drug is contraindicated in patients with known anaphylactic or severe systemic response to immunoglobulin.
Main drug interactions	The product may interfere with the response to live viral vaccines.
Main side effects	Allergic reactions, fever, nausea and vomiting, headache, back pain, and elevations of serum creatinine. Transmission of Creutzfeldt-Jakob disease and infections, aseptic meningitis syndrome, hemolysis, and thrombosis, as in the Pentaglobin therapy, are adverse effects listed earlier.

IFN-β

	A single-center phase II study demonstrated that antiviral treatment with IFN-β in patients with biopsy-proven enteroviral or adenoviral intramyocardial persistence may result in virus elimination and prevention or progression of left ventricular dysfunction [34]. Virus elimination was associated with hemodynamic and clinical improvement. A randomized placebo-controlled multicenter study was initiated in November 2002 to confirm the efficacy of IFN-β (Betaferon; Schering H.C., Berlin, Germany), and its results in chronic viral cardiomyopathy are awaited. It appears from preliminary data that soft parameters (eg, quality of life) improved; however, survival and ejection fraction did not improve.
Standard dosage	According to the study protocol, a stepped regimen should be followed to minimize the flu-like side effects of IFN-β in the initial phase of treatment. The initial dose is 2×10^6 U subcutaneously three times a week on alternate days. The dose is then increased to 12×10^6 U during the second and 18×10^6 U during the third week. The treatment should be continued for 6 months [34].
Contraindications	IFN-β is contraindicated in patients with a history of hypersensitivity to natural or recombinant IFN-β, in pregnancy, and in the nursing period. It should be used with caution in patients with a history of depression, suicide attempt, epilepsy, or myelosuppression.
Main drug interactions	No drug interaction studies have been conducted with IFN-β. However, combination with other immunosuppressive drugs, except for corticosteroids or adrenocorticotropic hormone, should be avoided.
Main side effects	The most serious adverse reactions are depression, suicidal ideation, and injection site necrosis. The most often observed adverse effects are leukopenia, fever, flu-like symptoms, injection site reaction, asthenia, headache, and increased liver enzymes.
Cost/cost-effectiveness	Relatively expensive: 15 ampoules of injectable powder cost 1399.54 euros. Each ampoule contains 9.6×10^6 U of IFN-β at a cost of 93.30 euros.

Immunosuppression

- The role of immunosuppression for the treatment of myocarditis is still controversial. The largest randomized, double-blind study, the American Myocarditis Treatment trial [35], did not show any benefit of immunosuppression with cyclosporine or azathioprine combined with prednisolone on mortality or left ventricular function after 6 months of treatment. However, this study was underpowered and did not distinguish viral from nonviral (autoreactive) myocarditis. In viral myocarditis, application of immunosuppression is most likely unfavorable because of augmentation of viral replication.

- A recent retrospective analysis of patients with active myocarditis examined the virologic and immunologic profile of responders and nonresponders to immunosuppression treatment [36]. Viral genomes in the myocardium were found in 85% of nonresponders compared with only 14% of responders.
- Immunosuppression cannot be recommended for the routine treatment of viral myocarditis. However, immunosuppressive therapy demonstrated a beneficial effect in patients with no detectable viral genome in endomyocardial biopsy (nonviral or autoreactive myocarditis) and elevated cardiac antibodies in the serum [36]. The ESETCID [32,33] randomized patients with virus-negative autoreactive myocarditis to immunosuppressive therapy with prednisolone and azathioprine or placebo. The results are awaited.

Interventional and surgical procedures

- Intra-aortic balloon pump counterpulsation, ventricular assist devices, and heart transplantation [37] are the last treatment options in critical cases with intractable cardiogenic shock. However, immunosuppression after transplantation in originally viral myocarditis may also lead to an ambiguous outcome.

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Papers of particular interest, published recently,
have been highlighted as:
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