

# Drugs and/or devices in dilated cardiomyopathy

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### Abstract

Dilated cardiomyopathy (DCM) is the most common type of nonischemic heart muscle disease, with a prevalence of 36 cases per 100,000 people. In contrast to other heart diseases it often affects the young and presents with reduced systolic function and ventricular dilatation due to infectious, toxic, metabolic, or genetic causes. Regardless of the underlying cause, patients are given standard medication for heart failure in order to improve cardiac function, treat symptoms, and prevent complications. Subgroups of patients with acquired infectious or postinfectious autoimmune diseases can be treated successfully if underlying causes have been characterized carefully.

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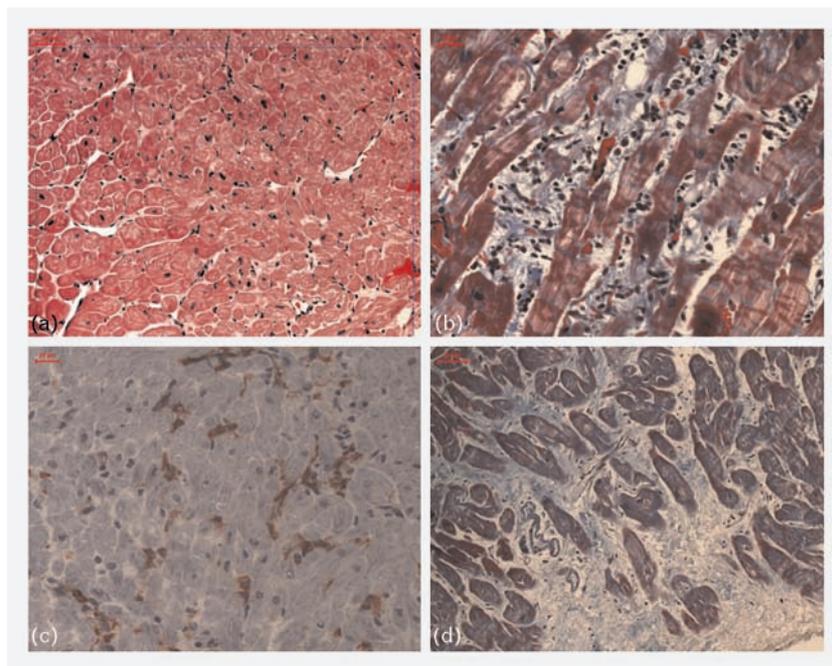
### Introduction

Dilated cardiomyopathy (DCM) is a cardiac muscle disease characterized by reduced contractile function and dilatation of the left or both ventricular chambers [1]. Aside from genetic inheritance and etiologically undefined “idiopathic” cases, DCM is often acquired and caused by infections or toxic agents (e.g., alcoholic cardiomyopathies), or associated with autoimmune diseases, pregnancy, systemic, and other cardiovascular disorders. Since the acquired causes constitute a sizeable proportion of DCM, the observed frequency of the undefined so-called “idiopathic” entities, last but not least, depends on the effort and technical means applied to come to a specific and reliable diagnosis [2,3]. This important issue notably concerns immune, autoimmune and infectious causes due to the fact that subgroups of patients may gain benefit from specific treatment strategies [4]. Uncovering such treatable causes of DCM demands, however, direct analysis of tissue samples obtained by biopsy, because non-invasive clinical tools do not

usually provide the required diagnostic accuracy to allow successful intervention (*Fig. 1*) [5,6].

### Symptomatic treatment of heart failure

Although conventional pharmacotherapy does not influence specific causes of acquired diseases of viral or immune origin, it remains the hallmark of any heart failure therapy [7]. It does not depend on the disease’s etiology and remains primarily supportive. Despite routine use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor (ABR) blockers, beta blockers, diuretics, and spironolactone in patients with heart failure due to DCM, these patients still have a considerable annual mortality rate of 5–10%. A survival benefit has been demonstrated for ACEinhibitors, beta blockers, and spironolactone, which should be administered routinely starting with low doses in all patients with New York Heart Association (NYHA) class II to IV heart failure [8]. Diuretics may improve heart failure symptoms without



*Figure 1. Histology of acute and chronic dilated cardiomyopathy (DCM)/inflammatory cardiomyopathy (DCMi) influencing treatment decisions. (a) Regular myocardial tissue without infiltrating inflammatory cells, fibroses or scars. (b) Active myocarditis. (c) Chronic DCMi without relevant fibrosis or scars. (d) DCM with myocyte hypertrophy and replacement fibrosis (scars). A significant number of patients without irreversible myocardial injury may improve spontaneously (a) or upon immunosuppressive treatment (b, c) if ventricular dysfunction is caused by an acute or chronic inflammatory process. In the later stage of DCM (d) specific treatment at best can prevent inflammation-associated progression of heart failure, but ventricular function will not recover.*

significant effect on long-term outcome. Despite improvements in the treatment of heart failure in the last 15 years, clinical outcome following the onset of symptoms has not substantially changed.

Cardiac transplantation has been considered the last treatment for end-stage heart failure, with DCM as one of the leading causes diagnosed at the time of the operation. Since the necessary number of organs is stagnating or has even declined in some countries over the past years, mechanical left ventricular assist device (LVAD) has been introduced as one promising option to improve prognosis until recovery from acute fulminant disease or to bridge to transplantation in end-stage disease (Fig. 1).

## Antiarrhythmic treatment

Due to their negative inotropic effects, most antiarrhythmic drugs, including newer substances such as dronedarone should be avoided in patients with severe systolic heart failure and an ejection fraction below 35% and acute or worsened heart failure (NYHA IV), respectively. Beta blockers or amiodarone can be used but have to be handled with care in these patients and may prevent sinus tachycardia and different forms of supraventricular or ventricular arrhythmias, respectively. In the long run, however,

drugs do not significantly reduce increased mortality due to sudden cardiac death (SCD) caused by tachyarrhythmias, ventricular tachycardia (VT), or ventricular fibrillation (VF). An implantable cardioverter-defibrillator (ICD) is established as the most reliable therapeutic tool and indicated for documented VT/VF or aborted SCD for secondary prevention. If patients with irreversibly impaired ventricles and left ventricular branch block are supplied with an ICD, it can be combined with cardiac resynchronization therapy (CRT) e.g., by biventricular chamber pacing. In early stages of acute disease or DCM due to acquired causes, a wearable defibrillator (LifeVest<sup>®</sup>) rather than a permanent device is a rational choice for patients with a temporary risk of sudden cardiac arrest to bridge the first critical period if spontaneous or treatment-associated recovery is expected.

## Biopsy-based specific treatment of acquired disease

The gold standard of diagnosing the underlying causes of infectious myocarditis and inflammatory cardiomyopathy (DCMi) is the histological, immunohistological and polymerase chain reaction (PCR)-based analysis of endomyocardial biopsies if its time-dependent and

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methodological limitations are kept in mind [9]. Both persistent viral infections and infection-associated or postinfectious inflammatory processes of the myocardium have been recognized as independent prognostic parameters—in addition to left and right ventricular dysfunction—in myocarditis and DCM [3,10]. Therefore, in addition to conventional pharmacotherapy specific treatment options are required that directly address the underlying viral or inflammatory causes of the disease (Fig. 1).

### Immunoadsorption

Persisting virus infections and postinfectious myocardial injury may produce antibodies that crossreact with myocardial antigens and the myocyte Fc-receptors thereby contributing to impairment of cardiac contractility [11,12]. Long-term reduction of such cardio-depressive antibodies from sera of patients with refractory heart failure as a result of DCM by immunoadsorption significantly improves ventricular function in many but not all patients [13,14]. The effect of immunoadsorption on longterm outcome is not currently known; a controlled treatment trial is currently being performed.

### Immunomodulatory treatment

Myocardial inflammatory processes or autoimmunity may survive myocardial virus elimination and warrant immunosuppressive treatment in order to prevent later immune-mediated myocardial injury, particularly in the aggressive forms of myocarditis such as giant cell granulomatous myocarditis (Table 1). Frequently administered anti-inflammatory drugs are immunoglobulins, corticosteroids, azathioprine and cyclosporine, which are administered on top of regular heart-failure medication.  $\alpha$ -Methylprednisolone is

generally given, at a rate of 1 mg/kg body weight, initially for 4 weeks. Depending on the body weight, 100 to 150 mg azathioprine daily can be administered in addition to the steroid medication. The steroid dosage is titrated biweekly in increments of 10 mg until a maintenance dose of 10 mg is reached. The treatment should last for 3 to 6 months. Current data from initial randomized trials confirm efficacy of those treatment regimens in carefully selected patients [15–17].

Both treatment of early disease with frequent spontaneous recovery and the lack of information on the actual virus state due to incomplete diagnostic accuracy have blurred the results of the initial randomized trials [18–20]. More recent studies with exactly characterized cohorts of patients have confirmed earlier data that patients with inflammatory cardiomyopathy respond well to immunosuppression if persistent viral infection is excluded before treatment [15–17].

### Anti-infectious treatment

Interferons (IFNs) serve as a natural defense against many viral infections. Their innate production is associated with clinical recovery from viral infection and subsequent sequelae while exogenous administration is protective. Type I interferons therefore constitute a promising choice for treatment for selected infectious agents.

Data from an IFN- $\beta$  phase II study provided first evidence that antiviral IFN- $\beta$  1a therapy effectively clears cardiac enterovirus and adenovirus infections in patients with chronic heart failure when given subcutaneously every other day in addition to constant heart failure medication [21]. The dosage  $4 \times 10^6$  IU and  $6 \times 10^6$  IU IFN- $\beta$  was well tolerated. After 24 weeks of treatment complete elimination of the viral genome was proven in follow-up biopsies in

Table 1. Immunosuppressive treatment of patients with myocarditis and inflammatory cardiomyopathy.

Muromonab (anti-CD3-antibodies) <sup>1</sup>	5 mg/day iv for 7 days	GCM
Methylprednisolone	10 mg/kg bw (first 3 days) then 1 mg/kg bw (see below)	
Ciclosporin <sup>2</sup>	Trough level: 100–150 $\mu$ g	
Azathioprine <sup>4</sup> (optional)	50–150 mg/day <sup>5</sup>	
Methylprednisolone <sup>3</sup>	1 mg/kg bw (4 weeks), tapering 10 mg for 6 to 12 months	GCM,
Pantoprazole	20 mg/day	Myocarditis: lymphocytic (auto-)immune eosinophilic granulomatous
Calcimagon D3 <sup>®</sup>	1 $\times$ 1/day	

Patients with giant cell myocarditis (GCM) should be treated with anti-CD3-antibodies, cortisone, and ciclosporin immediately after established diagnosis. Virusnegative DCMi or autoimmune myocardites, eosinophilic myocarditis, and granulomatous myocarditis such as sarcoidosis often respond to cortisone alone. Cortisone treatment may have to be replaced by other immunosuppressive drugs in case of side effects or may be extended by azathioprine, if necessary. In every case, therapy should be dispensed for about 6 months. <sup>1</sup>Attend initial hypotension and allergic reactions; <sup>2</sup>Control liver and kidney parameters; <sup>3</sup>Control blood count, glucose; <sup>4</sup>Control blood count, liver and kidney parameters; <sup>5</sup>Reduce or terminate if leukocyte counts <1000/nl or liver enzymes >3-fold normal value.

all patients. This was paralleled by a significant improvement in left ventricular function and ventricular size and amelioration of heart failure symptoms. None of the patients deteriorated. While entero- and adenoviruses seem to respond well to the interferon- $\beta$  treatment, subsequent open-labeled studies have shown that other viruses such as erythroviruses, including parvovirus B19, respond less well in terms of virus clearance, although erythrovirus load decreased and patients improved clinically. These data were confirmed by a first recently presented randomized IFN- $\beta$  treatment study (BICC-trial) [22]. The other viruses might respond in a better way to distinct anti-viral treatment regimens, but optimal treatment conditions for viruses other than enterovirus and adenovirus have not yet been defined. At present, antiviral therapy is still a matter of clinical trials in specialized centers.

## Conclusion

In acute DCM or DCMi, management is first of all supportive and does not aim at the causative agent. Rapid aggressive support of cardiac function including inotropic therapy, mechanical circulatory support, and arrhythmia management may be life-saving by bridging the interval for return to improved or native ventricular function or providing a bridge to transplantation. Generally a biopsy-based diagnosis is mandatory to initiate any specific treatment, in addition to standard heart failure therapy, in order to improve prognosis in patients with acute and chronic infectious and/or inflammatory disease. ■

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