

Viral heart disease — treatment

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INTRODUCTION

Acute myocarditis (MC) results in chronic cardiac dysfunction in 25% and in acute deterioration leading to death or end-stage dilated cardiomyopathy (DCM) in 12–25% of affected patients [1]. Patients with inflammatory DCM (iDCM) have worse outcomes than patients with non-inflammatory DCM.

Current European Society of Cardiology (ESC) guidelines on heart failure (HF) management recommend only standard treatment in viral heart diseases (VHD) [2]. However, recommendations on MC or viral cardiomyopathy (CM) consider several specific therapies requiring clear identification of the underlying aetiological factors and pathophysiology [1–3]. In contrast to the standard treatments, which mainly delay disease progression and do not affect the underlying infectious/inflammatory cause of the conditions, specific treatments can potentially prevent further tissue injury or even reverse the tissue damage [4–6]. In patients with irreversible damage of the myocardium, viral genome clearance and clinical stabilisation should be considered a therapeutic success [1, 3, 5, 7].

NON-SPECIFIC TREATMENTS IN VHD

Standard treatment regimens in patients with MC and HF symptoms include angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), beta-blockers, aldosterone antagonists, and diuretics [3, 4, 8]. The ideal duration of pharmacotherapy after restoration of left ventricular (LV) function has not been defined [1]. Patients with symptoms of arrhythmia should be treated according to the current ESC guidelines on ventricular arrhythmia and sudden cardiac death prevention [3, 9]. It should be remembered that most of the ventricular arrhythmias usually resolve after the acute phase of the disease.

Patients with acute and fulminant course of MC should be treated in highly specialised departments capable of performing and conducting expert analysis of endomyocardial biopsies [1, 9]. In cases presenting with cardiogenic shock or severe ventricular dysfunction, mechanical support with intra-aortic balloon pumps, LV assist devices, or extracorporeal membrane oxygenation may be required as a bridge to recovery or transplant [1, 8]. However, considering the high percentage of self-recovery, heart transplantation should be restricted to unstable patients not responding to treatment [1].

Several animal studies have investigated mechanisms related to the treatment of MC with non-specific agents. They reported both beneficial and even detrimental molecular effects.

ACEI, ARB

Captopril, olmesartan, and losartan effectively reduced inflammation, fibrosis, and cardiomyocyte necrosis in several murine models of viral and autoimmune MC [4, 8]. Candesartan improved survival (60% vs. 18%) in a murine model of viral MC [3, 8].

Diuretics

In a rat model of inflammatory CM torsemide delayed the progression to DCM and decreased fibrosis, cardiomyocyte hypertrophy, and the level of transformation growth factor beta, collagen II, and aldosterone synthase [4].

Beta-blockers

In a rat model of autoimmune MC, carvedilol, in contrast to metoprolol and propranolol, exerted immunosuppressive and antioxidant effects [4]. Treatment with metoprolol led to increased inflammation, cardiomyocyte necrosis, and mortality in a murine model of acute Coxsackievirus B3 (CVB3) MC [4]. There is insufficient human data, but it seems reasonable to avoid beta-blockers in the acute phase of decompensated HF and in the very early treatment of fulminant myocarditis [4].

Aldosterone antagonists

In a murine model of viral MC, eplerenone inhibited mast cell proteinases, and thereby decreased fibrosis [4].

Glycosides

Digoxin increased the level of the pro-inflammatory cytokines in a murine model of viral MC, and consequently increased mortality [4].

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (e.g. indomethacin) may be considered only in patients with myopericarditis, preserved or nearly preserved LV ejection fraction, and severe pleuritic chest pain [3, 4]. In several murine models of viral MC, non-steroidal anti-inflammatory drugs intensified inflammation and increased mortality [1, 3, 4]. Their use in MC is controversial and contraindicated in subjects with reduced LV ejection fraction (LVEF) [1].

Anti-thrombotic therapy

There are no guidelines or recommendations on anti-thrombotic therapy that specifically refer to VHD, probably reflecting the lack of randomised trials [1, 2]. Inflammation and HF itself are pro-thrombotic states [10]. Parvovirus B19 (PVB19) and human herpes virus 6 (HHV-6) activate the coagulation cascade by inducing tissue factor expression and by disrupting the endothelium [10]. There are no clear data on the benefits of anti-thrombotic therapy. Aspirin decreases platelet reactivity, but it is associated with increased inflammation and mortality in animal models of MC [10]. Heparin and fondaparinux in mouse models of MC reduced fibrosis but at the same time increased inflammation [10]. Therefore, anti-platelet and anti-coagulant drugs are not currently considered standard therapies in VHD.

Device therapy

Temporary pacing is required in cases of bradycardia and/or high-degree atrioventricular block triggering ventricular ar-

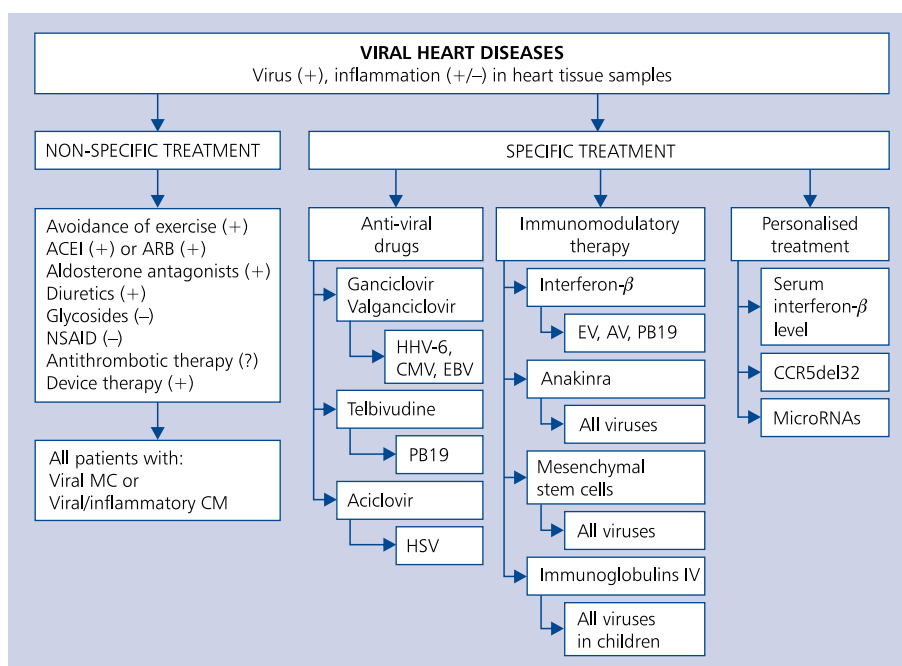


Figure 1. Viral heart disease treatment; abbreviations — see text

rhythmias in acute MC [9]. In cases of symptomatic sinus node dysfunction or atrioventricular block in the chronic phase of the disease, permanent pacemakers should be implanted [9].

Since self-recovery occurs in 50% of affected patients, cardioverter defibrillator implantation should be postponed until the chronic phase of the disease [1, 9]. Wearable cardioverter defibrillators seem to be a reasonable temporary option in acute MC with severe ventricular arrhythmias or severe LV dysfunction, although evidence is still lacking [1, 9]. The indications for cardioverter defibrillator implantation and cardiac resynchronisation therapy in inflammatory and viral CM are the same as for other aetiologies of HF [9]. Proper timing of device implantation is debatable [9]. It should presumably be postponed until specific treatments are completed.

Physical activity restrictions

Since physical activity increases viral replication and shortens survival, it should be restricted for at least six months in acute MC [1, 8].

SPECIFIC TREATMENTS IN VHD

Acute phase of the disease

Drugs influencing viral attachment to host-cell receptors, virus entry, and virus uncoating are being studied [3]. Pleconaril or soluble CAR-Fc might be effective in patients in the acute phase of the disease. However, these patients only represent a small percentage of patients requiring targeted therapy [3].

Chronic phase of the disease

The antiviral drugs (e.g. ganciclovir, telbivudine) affect the life cycle of the virus, whereas the immunomodulatory therapies: interferon-beta (INF- β), mesenchymal stem cells (MSC) and immunoglobulins (IVIG), support the immune response (Fig. 1).

Interferon beta

In response to viral entry into cells, IFNs type I (α and β) are being secreted in order to inhibit viral replication. Viruses are sensitive to IFNs to a different extent with the type of infected cell also playing an important role [11]. INF- β 1a was proven effective in patients with MC and CM induced by adeno- and enteroviruses in open non-controlled phase II trials and one randomised phase II trial [3, 6, 12]. A six-month treatment regimen of INF- β 1a led to myocardial virus elimination in all patients, and improvement of both clinical (New York Heart Association [NYHA] functional class) and haemodynamic (LV dimensions and LVEF) parameters in almost all patients [8, 13]. Changes were more pronounced in patients with global wall motion abnormalities, compared with patients with regional dysfunction. Interestingly, the prognosis after INF- β 1a treatment-based enterovirus clearance was better than that in patients with spontaneous enterovirus clearance [13]. In most cases of CM and MC due to PVB19 and HHV-6 infection, the virus was not eliminated but its load was reduced, with improvement of endothelial function and symptoms [14].

Table 1. Therapeutic options for viral and virus-negative cardiomyopathies

Indication	Drug	Dose	Laboratory tests	Caution
Enteroviral or adenoviral cardiomyopathy	INF- β 1	Different treatment regimens: 1 st week 2×10^6 IU subcutaneously every 48 h, 2 nd week 4×10^6 IU every 48 h, 3 rd –24 th week 6×10^6 IU every 48 h [4] or 8×10^6 IU every 48 h [20] or 1 st week 2×10^6 IU every 48 h followed by 4×10^6 IU every 48 h or 1 st week 2×10^6 IU every 48 h, 2 nd and 3 rd week 4×10^6 IU every 48 h followed by 8×10^6 IU every 48 h [9]	2 weeks after treatment initiation and monthly (CK, CK-MB, Tnl/TnT, blood count, creatinine, liver enzymes, TSH/T3/T4) [31]	Treatment termination if platelets below $100,000/\mu\text{L}$ or leukocytes below $2000/\mu\text{L}$ [31]
PVB19 cardiomyopathy	INF- β 1	Different treatment regimens: 1 st week 2×10^6 IU subcutaneously every 48 h, 2 nd and 3 rd week 4×10^6 IU every 48 h, 4 th –24 th weeks 6×10^6 IU every 48 h [4] or 1 st week 2×10^6 IU followed by 4×10^6 IU or 1 st week 2×10^6 IU, 2 nd and 3 rd week 4×10^6 IU followed by 8×10^6 IU [31]	2 weeks after treatment initiation and monthly (CK, CK-MB, Tnl/TnT, blood count, creatinine, liver enzymes, TSH/T3/T4) [31]	Treatment termination if platelets below $100,000/\mu\text{L}$ or leukocytes below $2000/\mu\text{L}$ [31]
	Telbivudine	600 mg once daily orally for 6 months [29]		
HHV-6 cardiomyopathy	Ganciclovir/ /valganciclovir	1000 mg intravenously every 24 h for 5 days followed by 900 mg of oral valganciclovir up to 6 months; 1800 mg daily in case of symptom recurrence [31]	2 weeks after treatment initiation (blood count, creatinine, liver enzymes) [31]	Treatment termination in cases of neutropenia, anaemia, hepatitis [31]
HSV-DCM	Aciclovir	500 mg intravenously every 8 h for the first 5 days and then 9 days orally 400 mg every 4 h except one dose at night [28]		

INF- β — interferon β ; CK — creatinine kinase; CK-MB — creatinine kinase MB isoenzyme; Tnl — cardiac troponin I; TnT — cardiac troponin T; TSH — thyroid stimulating hormone; T3 — triiodothyronine; T4 — thyroxine; PVB19 — parvovirus B19; HHV-6 — human herpes virus 6

The drug is administered subcutaneously every other day for 24 weeks (see details in Table 1). Its main adverse effects in the first four weeks include fatigue, parainfluenza symptoms, and erythema at the site of injection, which generally resolves after 1–2 days [3]. In patients with severely depressed LV systolic function (LVEF $\leq 30\%$), mild exacerbation of HF symptoms often associated with LV dilatation and deterioration of LVEF may occur between the 4th and 12th week of treatment [3]. Usually, signs resolve gradually within one to two weeks of therapy followed by direct and continuous recovery in 40% of patients. For 25–30% of patients, recovery is delayed for two to four months [3].

A randomised, double-blinded, multicentre, placebo-controlled phase II trial BICC-Study (Betaferon in patients with chronic CM) included 143 patients with symptomatic

chronic HF (both with impaired and preserved LVEF) and enterovirus, adenovirus and/or PVB19 genome in the myocardial tissue treated with IFN- β -1b vs. placebo for 24 weeks [4, 6, 12]. The treatment was well-tolerated and safe [6]. Compared to controls, significantly more patients treated with IFN- β 1b achieved viral elimination and/or viral load reduction (OR 2.33, $p = 0.048$) [6, 12]. Treatment also resulted in improvement of at least one NYHA class (38.6% vs. 18.6%, $p = 0.013$) and quality of life ($p = 0.032$) [6, 12]. The improvement in NYHA functional class and quality of life were more pronounced in the group of patients with enterovirus/adenovirus infection in comparison to those with PVB19 infection [6]. Symptomatic improvement was also observed in patients with PVB19 load reduction, probably due to PVB19 transcriptional activity silencing [6]. Transcriptionally active PVB19 is associ-

ated with a higher rate of dyspnoea, fatigue, and angina. The number of circulating apoptotic endothelial cells is reduced, while the number of circulating progenitor cells is increased [14]. IFN- β 1b improves endothelial cell survival and replication [6].

Ganciclovir/valganciclovir

Most of the patients with HHV-6-induced VHD are infected with HHV-6B (which infects endothelial progenitor cells) rather than with HHV-6A (which infects neural cells) [15, 16]. It is highly probable that HHV-6 enhances pathogenicity of other viruses [15]. In some patients, HHV-6 virus is chromosomally integrated (ciHHV-6 — identification by repeated measurement of viral loads above 10^4 DNA copies per μg of isolated DNA in tissue or blood cells) [3, 15, 16]. ci-HHV-6A is probably associated with an increased risk of MC [3, 15, 16]. HHV-6 is not cleared by IFN or ganciclovir (herpesvirus-specific inhibitor of replication) [16]. Intravenously administered ganciclovir for 10 days followed by oral valganciclovir for six months in MC, viral CM, and ciHHV-6 HF patients improved the clinical condition and echocardiographic parameters (Table 1) [16]. Patients reported a rapid improvement of symptoms after two weeks of treatment [16], which is probably due to the elimination of DNA replication and RNA synthesis [16].

Myocarditis induced by cytomegalovirus (CMV) in an immunocompetent host is exceedingly rare [17]. Due to the self-limiting character of the disease and the potential toxicity of valganciclovir, its administration in CMV MC is questionable [17]. Valganciclovir might be beneficial in patients with a fulminant course of the disease and multi-organ involvement [17]. Epstein-Barr virus (EBV) and CMV-induced inflammatory or viral CM could potentially be treated with valganciclovir; however, data guiding treatment decisions are sparse [3].

Aciclovir

The herpes virus simplex (HSV) genome is detected in less than 1% of patients with MC, and is absent in patients with DCM [18]. Aciclovir may be considered in patients with HSV-induced MC [1]. There are only a limited number of cases reported of HSV-induced DCM successfully treated with aciclovir [18].

Nucleoside analogues

Due to the limited efficacy of INF β in PVB19 infection, searches for new therapeutic options are ongoing. It was proven, in vitro, that telbivudine, a thymidine analogue inhibiting DNA polymerase, suppressed PVB19 replication and reduced apoptosis of circulating angiogenic cells. Kühl et al. [19] tested telbivudine in a group of eight patients with PVB19-associated chronic MC. After a treatment period of 24 weeks, PVB19 transcription silencing and significant viral load reduction could be demonstrated in seven patients [19].

NYHA class (median: 3–2, $p < 0.05$) and quality of life (38.5 vs. 14.5, $p < 0.05$) were significantly improved, while LVEF increased (45% vs. 55%, $p < 0.05$) and six-minute walk distances were prolonged (486 m to 563 m, $p < 0.005$) [19]. These results make telbivudine an interesting potential therapeutic option [19]. Currently, results of a larger trial are awaited.

Anakinra

Interleukin-1 (IL-1) plays an important role in the pathogenesis of MC [20]. The release of intracellular contents of dying cardiomyocytes activates the release of active IL-1 from inflammatory cells, causing uncontrolled inflammation [20]. Even very low concentrations of IL-1 suppressed the contractile function of cardiomyocytes in ex vivo studies [20]. Cavalli et al. [20] administered anakinra, an IL-1 receptor antagonist, 100 mg daily subcutaneously in a patient with viral fulminant MC not responding to standard pharmacological and mechanical treatment. IL-1 inhibition resulted in rapid clinical and haemodynamic improvement [20]. Injection site reactions and neutrophilia are possible adverse effects of anakinra [20]. It should be noted that endomyocardial biopsy was not performed for this reported case [20].

Mesenchymal stem cells

Mesenchymal stem cells (MSC) are a heterogenous population of cells located mainly in the perivascular niches in almost all tissues [21]. MSC migrate to the site of inflammation, where the local micro-environment and cytokines (IFN- γ , tumour necrosis factor α [TNF- α], IL-1 α , or IL-1 β) activate their immunomodulatory effects [21]. MSC modulate the function of a great variety of immune cells [21]. MSC promote a Th2 phenotype, which is of great relevance for preventing the development of autoimmune heart disease. The formation of CD8+ T cells is inhibited, but activated CD8+ T cells are preserved with restricted killing of virally infected cells [21]. The generation of T regulatory cells is favoured, which ultimately leads to immune tolerance [21]. In the presence of MSC, plasmacytoid dendritic cells upregulate the release of the anti-inflammatory and cardioprotective cytokines IL-10 and IFN type I [21]. Generation of anti-inflammatory macrophages is encouraged, which is relevant for resolving the inflammation and for the prevention of the development of autoimmune MC [21]. The production and activity of cytokine-induced proliferation of natural killer (NK) cells, granzyme B release, and receptor expression are inhibited [21]. Because NK cells have cardio-protective activity through the release of IFN- γ , MSC administered in the early stage of viral infection could favour viral replication [21]. MSC-mediated inhibitory effect on NK cells could be beneficial by reducing myocardial damage in the case of NK cell over-activation and persistence in the myocardium in the subacute phase of MC [21]. B-cell proliferation and differentiation to antibody secreting cells is

inhibited, which could be beneficial in the subacute phase of MC [21]. MSC decreases fibroblast proliferation and collagen I and III expression, and promotes extracellular matrix metalloproteinase secretion [21]. Angiogenesis is promoted by the secreted proangiogenic factors, and the ability of MSC to differentiate into endothelial cells [22]. MSC in vitro reduced the apoptosis of CVB3-infected cardiomyocytes, reactive oxygen species production, and viral progeny release [22]. In the murine model of acute CVB3-induced MC, MSC improved cardiomyocyte contractility, decreased fibrosis, and reduced activation of CD4+ and CD8+ T cells [22]. The cardiac viral load was, however, not decreased. MSC have the ability to migrate to the injured tissue, and can be administered intravenously.

Intravenous immunoglobulins

Intravenous immunoglobulins (IVIG) exert antiviral and immunomodulatory effects in patients with viral MC/inflammatory CM [1]. However, in the Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) trial of recent-onset DCM, an improvement in LVEF was not observed [1, 8, 23]. Better therapeutic results were achieved in children with acute MC [3, 8]. Investigations comparing IVIG with steroid therapy in acute MC showed no additional benefit [3]. Therefore, IVIG therapy is currently not recommended in viral and autoimmune MC/CM [1, 8].

Immunoabsorption

Experimental and clinical data suggest that activation of the humoral immune system with production of circulating cardiac autoantibodies also plays an important role for the progression from MC to iDCM and for further progression of cardiac dysfunction [24]. Small, open, controlled or uncontrolled studies showed that removal of circulating antibodies by unspecific immunoabsorption with subsequent IVIG substitution (IA) results in improvement of cardiac function, better exercise capacity, and a decrease in myocardial inflammation [25, 26]. IA has also been shown to be related to alterations of the cellular immune response. Thus, a decrease of activated T-cells as well as an increase of regulatory T-cells revealing a link between cellular and humoral immunity has been found after this treatment [27]. Whether IA represents a therapeutic option for patients with iDCM for improvement of cardiac function is currently being investigated by a large placebo-controlled multicentre study (ClinicalTrials.gov Identifier: NCT00558584).

PERSONALISED THERAPY

There are increasing data on personalised treatment in MC and viral CM. Based on the following information, specific treatments can be initiated earlier, and minimise tissue injury [28].

Serum IFN- β levels are significantly elevated in patients with spontaneous enterovirus clearance, in comparison with patients with enterovirus persistence [13]. IFN- β measure-

ment, therefore, could indicate patients with reduced IFN- β levels, who require immediate IFN- β therapy.

A 32-base pair deletion (del32) in the gene encoding CC chemokine receptor 5 (CCR5) results in its deficiency [29]. In patients with clinically suspected MC or DCM, CCR5del32 polymorphism is associated with reduced mortality [29]. A strong correlation between CCR5del32 genotype and spontaneous virus clearance in patients with enteroviral CM has been demonstrated. Therefore, CCR5 or CCR5 gene might be possible drug targets in MC and viral CM.

MicroRNAs (miRNAs) are short non-coding RNAs, which are transported out of the nucleus into the cytosol where they influence translation. They affect all biological processes including cardiomyocyte proliferation, angiogenesis, fibrosis, and cell death. MiRNA profiling allows the identification of patients with CVB3 infection, who will benefit from INF- β administration, and those who will spontaneously eliminate the virus [28, 29]. Latent and reactivated PVB19 infection are characterised by distinct miRNA expression profiles [30]. No evidence of virus transcriptional activity (no detection of virus-encoded VP1-VP2-mRNA) also indicates latent virus replication with no pathogenic relevance [31]. PVB19 load was not shown to influence survival in patients with DCM [32].

CONCLUSIONS

Although the mainstay of treatment for viral heart diseases is standard HF therapy, increasing evidence suggests that greater emphasis should be put on causal and personalised treatment options. Patients should be identified and treated at early reversible stages of the disease course. Ongoing randomised clinical trials on specific therapies in VHD may change future ESC guidelines on management of VHD.

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