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Myocarditis: the immunologist's view on pathogenesis and treatment

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Summary

Viral myocarditis is a frequent and often unrecognised cause of post-inflammatory cardiomyopathy. The role of viral persistence and heart-specific autoimmunity in the development of myocarditis and heart failure is still controversial. This review updates the current view on the immunological mechanisms of disease development and addresses the current and future role of immunomodulation and immunosuppression as treatment options for defined subgroups of patients with myocarditis or dilated cardiomyopathy.

Key words: myocarditis; cardiomyopathy; autoimmunity; immunosuppression; immunomodulation; heart failure

Introduction

Clinical symptomatic myocarditis, ie inflammation of the heart muscle, is not a common diagnosis. Nevertheless, epidemiological data suggest that myocarditis is an important cause of sudden death in the younger population [1, 2]. Furthermore several lines of evidence imply that most cases of dilated cardiomyopathy [3], the most common cause of heart failure and transplantation in children and patients below the age of 40, are the consequence of a preceding myocarditis.

Disease course

Myocarditis represents a clinically and pathogenetically highly variable disease entity. Whereas some patients follow a fulminant disease course with acute heart failure and severe arrhythmias, most present with minimal symptoms or are entirely asymptomatic. Nevertheless, even asymptomatic patients are at risk for unexplained sudden death. In fact, data from necropsy studies suggest that undiagnosed or asymptomatic myocarditis is not a rare cause of death with the prevalence up to 1% [4].

Etiology

Worldwide, infections with the parasitic protozoan Trypanosoma Cruzi (Chagas disease), which is endemic in Southern America, are the leading cause of myocarditis [5]. In Europe and North America, however, enteroviruses, such as Coxsackievirus B3 [6–8] and to a lesser extent Adenovirus [4, 8], have been suggested as the most common micro-organisms inducing inflammatory heart disease. Other common cardiotropic micro-organisms include Cytomegalo- [8, 9], Parvo- [8, 10], Hepatitis C- [11, 12], Human Immunodeficiency- [13] and Epstein-Barr Virus [12, 14]. Recent findings, however, suggest that cardiotropic bacteria such as Chlamydia Pneumonia or Borrelia Burgdorferi might play a yet underestimated role in the development of post-inflammatory heart failure [8].

Non-infectious myocarditis denotes cardiac inflammation with no evidence of myocardial infection, for example in the context of autoimmune

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diseases, drug-induced hypersensitivity, neoplasia and/or other systemic disorders [6, 15]. Giant-cell myocarditis is a rare, idiopathic and histological distinct disease entity with a very poor prognosis, which often affects patients with latent or symptomatic autoimmune diseases [16].

Pathogenesis

How is the myocardium affected by viral infections? First, virus infection directly contributes to cardiac tissue destruction by cleaving the cytoskeletal protein dystrophin, leading to a disruption of the dystrophin-glycoprotein complex [17]. It is hypothesised that this mechanism is crucial for enteroviral replication in the heart and for the development of viral associated chronic cardiomyopathy [17]. If extensive damage occurs, it is conceivable that the heart is functionally impaired and heart failure develops. This might be the case during fulminant myocarditis. Interestingly, patients with fulminant myocarditis that survive acute disease and probably clear the virus do not develop progressive heart failure [18].

In mouse strains, susceptible and resistant to chronic myocarditis, viral genome and transcript are present. This indicates that the persistence of virus alone may not be the single determining factor in the development of chronic cardiomyopathy and that the viral damage itself may not be as important as the viral associated immune response [19]. Indeed it appears that progression to overt heart failure reflects an ongoing process due to the development of heart-specific autoimmunity, virus persistence or both. In this context several clinical studies and insights from animal models provide evidence that autoimmune mechanisms significantly contribute to chronic cardiac inflammation. Autoimmune features in patients with inflammatory cardiomyopathy include familiar aggregation, abnormal expression of HLA-class II on cardiac endothelial cells, a weak but significant association with HLA-DR4 and the detection of organ- and disease-specific autoantibodies of the Ig G class by indirect immunfluorescence (IFL) in approximately 30% of patients with myocarditis and dilated cardiomyopathy [20–23]. Two of the autoantigens recognised by the antibodies found by IFL could be identified as alpha and beta myosin heavy chain isoforms [23]. The low frequency of cardiac specific autoantibodies in patients with heart failure not due to myocarditis or dilated cardiomyopathy, the decrease of autoantibody titers during disease progression in dilated cardiomyopathy and the deterioration of cardiac function in myosin antibody positive patients indicate that these antibodies are not merely an epiphenomenon but represent specific markers of immune pathogenesis [23, 24]. Animal models further support the idea that autoimmune mechanisms triggered by viral infection contribute to the pathogenesis of inflammatory and post-inflammatory cardiomyopathy. Comparable to human myocarditis infection of genetically defined mice strains with cardiotropic virus results in ongoing myocarditis and dilated cardiomyopathy [25]. Development of myocarditis is associated with polyclonal heart-specific autoantibody responses and heart-specific, autoaggressive T cell responses [19, 26]. The evidence available indicates a key role for alpha-myosin as a target antigen in development of myocarditis and dilated cardiomyopathy as the same susceptible mouse strains develop autoimmune myocarditis in the absence of virus infection after immunization with activated dendritic cells loaded with alpha-myosin peptide [27]. The finding that in some susceptible mouse strains like DBA/2 mice virus- or myosin-induced myocarditis is an antibody-mediated disease may also apply to humans which means that the heart-specific antibodies may be directly pathogenic in some patients with myocardits and dilated cardiomyopathy [23, 24]. In this context further randomised studies examining the therapeutic value of non-antigen-specific Ig G adsorption [28] as well as antibody-specific plasmapheresis and affinity adsorption are needed.

Taken together it is still a matter of debate, whether the presence of persistent virus by itself or infection-triggered autoimmunity is of more relevance to the development of heart failure. In order to refine current treatment strategies it is more important to define diagnostic criteria that allow us to recognise which mechanism is of relevance in the setting of an individual patient.

Diagnosis

A diagnosis of myocarditis most often results from patient history and the exclusion of other heart diseases, most importantly coronary artery disease. Mainly patients who are suspected of myocarditis presenting with rapidly deteriorating left ventricular function and severe arrhythmias and also those with a history of a dilated cardiomyopathy not corresponding to best medical treatment should be considered for endomyocardial biopsy. Despite its low sensitivity, mainly due to sampling errors, endomyocardial biopsy still represents the diagnostic gold standard [6, 29] as a definite diagnosis of myocarditis requires the detection of inflammatory infiltrates and myocyte damage ac-

cording to the Dallas criteria [30]. Yet there are no universally accepted diagnostic criteria based on immunostaining for activation markers on inflammatory cells. The increasing sensitivity of molecular techniques, such as polymerase chain reaction (PCR), gene sequencing and real time PCR, improved the detection of viral genomes. Detection is now possible in small endomyocardial biopsies from patients with myocarditis but also in biopsies from patients with dilated cardiomyopathy without other evidence for inflammatory infiltrates [4, 7]. The latter finding reflects both, the low sensitivity of the histological analysis to detect subtle inflammatory infiltrates in endomyocardial biopsies and the fact that viral genomes can persist in the absence of ongoing inflammation. In future the additional use of new cell isolation techniques like the Laser Capture Microdissection (LCM) that offers the selection of antibody-targeted T lymphocytes and cardiomyocytes from a section of complex, heterogeneous cardiac tissue may ameliorate the read-out of endomyocardial biopsies combining the sensitivity of PCR analysis with the option for cell localization of the infectious agent [31].

Supportive treatment

Over the last years myocarditis therapy has been restricted to supportive options facing the clinical syndroms of heart failure or arrhythmias [6], including basic medications with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blocking agents, diuretics, beta-blockers and Amiodarone. Patients with persistently impaired cardiac ejection fraction and/or life threatening arrhythmias take survival advantage from ventricular assist devices and implantable cardiac defibrillators (ICD). In severe and rapidly progressive cases, however, heart transplantation still represents the only therapeutic option.

Immunosuppression

The idea that autoimmune mechanisms play an important role in the pathogenesis of myocarditis and post-viral cardiomyopathy has suggested a potential beneficial effect of immunosuppression in affected patients. Unfortunately, large randomised clinical trials have failed to prove that immunosuppression indeed improves survival in myocarditis [32, 33], The largest study, the Myocarditis Treatment Trial [33], did not show beneficial effects of a combined immunosuppressive regimen on primary endpoints such as left ventricular function or survival. However, inclusion criterion was a histological diagnosis of myocarditis according to the Dallas criteria without further risk stratification for virus persistence and markers of immunoactivation on biopsy samples or cardiac autoantibodies. In contrast, several just recently published studies showed beneficial effects of immunosuppressive treatment for certain subgroups of patients with myocarditis. A large retrospective multi-centre study suggested that an immunosuppressive treatment regimen combining Cyclosporine and/or Azathioprin with corticosteroids improved outcome such as time to death or transplantation for patients with histological proven Giant-cell myocarditis [16]. In a prospective single centre study immunosuppression together with a gluten-free diet improved left ventricular function and clinical status of patients with Celiac disease-associated myocarditis [34]. Another study on patients with impaired cardiac function for more than 6 months and biopsy-proven active lymphocytic myocarditis suggested a favourable effect of immunosuppression for patients with no detectable viral genome on heart biopsy samples but elevated titers of cardiac autoantibodies in the serum [12]. Interestingly, the same study revealed a good response to immunosuppressive therapy for patients with Hepatitis C Virus-related myocarditis. In addition, a large randomised, prospective 2-centre study on patients with dilated cardiomyopathy selected for HLA upregulation as a marker for immunoactivation on endomyocardial biopsy samples showed beneficial effects of a combined immunosuppressive therapy regarding ejection fraction, end-systolic and end-diastolic dimensions as well as NYHA score after 24 months of treatment [35]. Of note, functional improvement always became evident within the first months of immunosuppressive treatment in most responders. Despite these encouraging data, however, there is no evidence so far that immunosuppression has a beneficial effect on primary endpoints, such as heart transplantation or death.

Immunomodulation

Based on findings from animal models of viral or autoimmune myocarditis [36–38] it was tempting to speculate that strategies either specifically targeting pro-inflammatory cytokines or specifically enhancing the anti-viral immune response might affect the outcome of patients with

myocarditis or post-inflammatory dilated cardiomyopathy. In this context, a prospective single centre phase II study recently found that Interferon-beta treatment of patients with dilated cardiomyopathy and myocardial enteroviral or adenoviral persistence resulted in elimination of viral genomes in all patients and improvement of cardiac function in more than 60% of the study population, mainly if suffering from a moderately decreased left ventricular function, after 24 weeks of treatment [39].

Patients with advanced heart failure show increased serum levels of the pro-inflammatory cytokine TNF-alpha. TNF-alpha is crucial for the development of autoimmune myocarditis in animal models [36]. Given the clinical availability of potent TNF-alpha antagonists it has been expected that these drugs might offer a promising therapeutic option for patients with myocarditis or dilated cardiomyopathy. Unfortunately, two large-scale, randomised clinical trials evaluating the TNF-alpha-antagonists Etanercept and Infliximab for the treatment of dilated cardiomyopathy had to be stopped early because of excessive mortality in the treatment arms [40, 41]. Therefore the effect of TNF-alpha antagonists has never been assessed in patients with biopsy proven myocarditis. Nevertheless, TNF-alpha antagonists cannot be recommended for the treatment of patients with myocarditis and are clearly contraindicated for patients with dilated cardiomyopathy. However, these negative findings do not exclude the possibility that strategies blocking other pro-inflammatory cytokines mediating cardiac inflammation, such as Interleukin-1 beta and Il-1 receptor antagonists, might show beneficial effects in the future.

Of note, several commonly used cardiovascular drugs also exhibit immunomodulatory properties. Data on rats and mice with autoimmune myocarditis suggest antiinflammatory and disease ameliorating potency for the beta-blocking agent Carvedilol [42], the antiarrhythmic drug Amiodarone [43] and for the ACE inhibitor Captopril but not for other ACE inihibitors [44, 45]. Furthermore a prospective clinical study on patients with idiopathic dilated cardiomyopathy has shown significant improvement in NYHA-classification and left ventricular function after a 14 weeks treatment with the HMG-CoA-reductase-inhibitor Simvastatin [46]. The effect of improved cardiac function might be due to changes in inflammatory cytokine patterns as decreased plasma concentrations for TNF-alpha and Interleukin-6 have been found.

Conclusions

Taken together, recent clinical and experimental data suggest that immunosuppression might become a reasonable option for defined subgroups of patients with myocarditis or dilated cardiomyopathy. Figure 1 summarises an updated approach that integrates the current level of clinical evi-

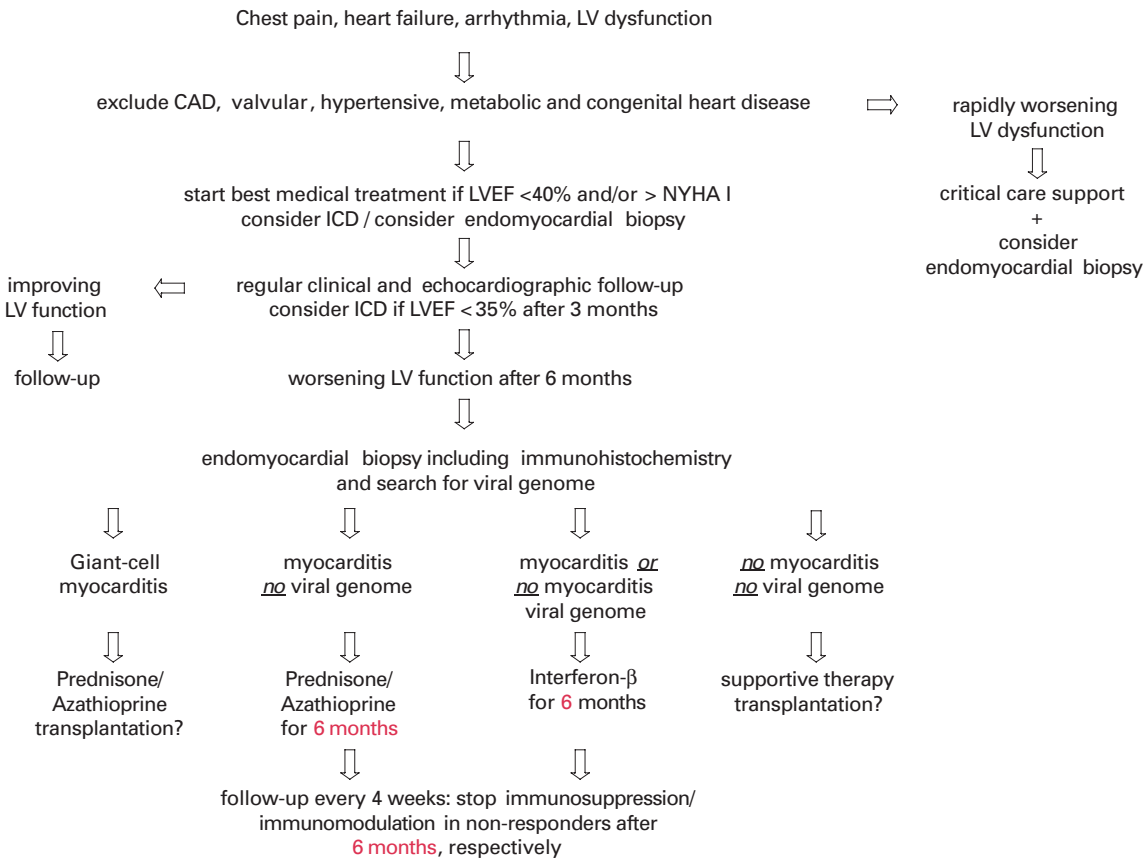

Figure 1.

Work-up if myocarditis is suspected. LV-dysfunction: left ventricular dysfunction; LVEF: left ventricular ejection fraction; CAD: coronary artery disease; ICD: implantable cardiac defibrillator

dence, expert opinion and insights from animal experiments. Because the selection of potential treatment responders requires invasive diagnostic approaches, elaborated immunological and microbiological analysis and thorough clinical evaluation, we recommend that patients with myocarditis and worsening cardiac function get a multidisciplinary work-up involving cardiologists, pathologists, immunologists and specialists in general internal medicine. Whenever possible, patients should be enrolled in ongoing treatment trials, such as the ongoing European study of epidemiology and treatment of cardiac inflammatory diseases (ESETCID) [8]. Together with experimental data on animal models, the completion of these trials will further clarify the role of immunosuppression/immunomodulation in defined subgroups of patients in the future.

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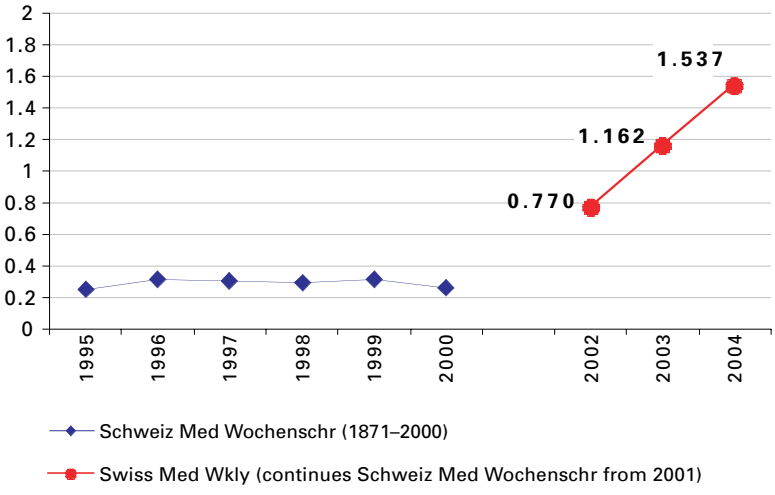

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