Advanced diagnostics in inflammatory cardiomyopathy for personalized therapeutic decision-making

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Pathological mechanisms of viral and postinfectious autoimmunity in myocarditis and inflammatory cardiomyopathy. A genetic predisposition is supposed for persistence of virus and/or inflammation. Advanced diagnostics including endomyocardial biopsies are essential for a pathologically-proven diagnosis as the basis for a specific, causal and personalized therapy.

Myocarditis (MC) and dilated inflammatory cardiomyopathy (DCMi) are the underlying cause of acute and chronic heart failure and sudden cardiac death. MC/DCMi represent many diseases with distinct immunophenotypes and/or viral infection, and present with various clinical manifestations ranging from asymptomatic courses to symptoms of chest discomfort, progressive heart failure, and to fulminant forms with cardiogenic shock or life-threatening ventricular arrhythmia. Due to the highly variable pathoaetiology, these diseases are
severely underdiagnosed. Although some patients with MC/DCMi recover spontaneously (40–50%), 25% progress to chronic inflammatory heart disease, and 12–25% may die or deteriorate to end-stage dilated cardiomyopathy (DCM), sometimes years later.1

Personalized specific management is only possible based on endomyocardial biopsy (EMB) analyses, which is the gold standard for definitive diagnosis of disease entities.2 In particular, it allows exact determination of the cause of disease (i.e. viral infection or immune-mediated MC/DCMi), and definition of the type of inflammatory process (active, chronic, or resolved) and characterization of the virus including replicative activity.3,4 The diagnosis of the specific aetiology (infectious vs. non-infectious and intensity and quality of inflammation) determines prognosis and is the basis for therapeutic decision-making. This indicates that the treatment of MC/DCMi should include two elements: optimal heart failure therapy, which does not influence the underlying cause of the disease, and application of disease-specific therapies based on EMB results.2,5 Since the pathophysiological changes of MC/DCMi occur at cellular and subcellular levels, imaging technologies, including cardiovascular magnetic resonance (CMR), cannot replace EMB as they cannot detect or distinguish different viral types or subtypes, active viral replication, or the degree and quality of inflammation. Therefore, EMB and CMR results have a poor overlap, rendering them not interchangeable in terms of interpretation, relationship with myocardial injury, and clinical outcome.

The position statement of the European Society of Cardiology recommends the individualized use of immunosuppression in lymphocytic MC/DCMi, after ruling out any viral infection on EMB by PCR analysis, as a retrospective analysis of patients with DCMi showed that patients with persistent viral infection did not improve or even deteriorated under this therapy.2 The recommendations are based on the findings of the first prospective randomized study on this topic, the TIMIC (Tailored Immunosuppression in Inflammatory Cardiomyopathy) study,6 performed in 2009 by A. Frustaci et al., one of the pioneers in myocarditis therapy research.

In this issue of the European Heart Journal, Chimenti and colleagues analysed long-term data of patients originally recruited in the TIMIC trial.7 Eighty-five patients with EMB-proven virus-negative chronic DCMi were enrolled and received prednisone and azathioprine vs. placebo for 6 months. Chimenti et al. described a long-term efficacy of immunosuppression in DCMi on cardiac dimension and function and on heart failure symptoms over a very long follow-up period (up to 20 years). Similar functional improvements also persisted over time in patients with severe left ventricular dilation and dysfunction at the time of diagnosis. The study further demonstrates the effectiveness of immunosuppressive therapy in patients initially allocated to the placebo branch of the trial who were subsequently given immunosuppressive treatment at study completion as a result of the documented superiorit y of the treatment regimen. The study observations support the presence of persisting focal myocardial inflammation in the enrolled patients that does not resolve spontaneously or with supportive therapy alone. Another point to discuss is that the majority of patients in the study showed significant improvement in heart size and function with restoration of normal cardiac output, while others did not respond. In a follow-up study, Chimenti et al. identified Toll-like receptor (TLR) 4, a known regulator of the innate immune system in the induction and perpetuation of inflammation in autoimmune diseases, as being highly expressed in non-viral myocarditis patients responding to immunosuppression.8 This highlights the critical importance of identifying novel biomarkers capable of predicting response to immunosuppressive treatment in eligible patients. Meanwhile, several studies have confirmed the efficacy of immunosuppressive therapy in patients with non-viral DCMi.9,10 The specific time point when therapy should be withdrawn after left ventricular ejection fraction recovery is not well defined and should be adjusted individually. Follow-up evaluation should be based on clinical and echocardiographic assessment, and a follow-up EMB may also be considered to determine duration of therapy.

**Future directions**

Numerous aetiological factors including host genetic susceptibility trigger the innate immune response and complex pathophysiological mechanisms maintaining and driving the cascade of inflammation.8,11,12 These data implicate that in most non-infectious cases, MC/DCMi is based on (auto-) immune-mediated mechanisms. It is considered possible that at some point in progression, multiple aetiological types conflate to form a common autoimmune pathogenic process that leads to chronic inflammation, tissue remodelling, and ultimately progression to the clinical phenotype of DCM. In this context, myocardial inflammation may also be crucial for the progression of genetic cardiomyopathy.13 Identifying the molecular basis for the differences in genetic susceptibility between individuals is a challenge for the future and may open up new opportunities for an individualized therapeutic approach.

Among non-infectious causes, immune-mediated mechanisms may develop, either as isolated cardiac involvement or in association with systemic diseases, including a broad spectrum of autoimmune and autoinflammatory diseases such as sarcoidosis, eosinophilic granulomatosis, lupus erythematosus, and scleroderma.1,5 Of particular note is autoimmune MC, which can develop in response to checkpoint inhibitor therapy. Toxic MC has been shown to be more common and severe than expected, although it may also respond to steroids.5 A total of 20% of giant cell myocarditis (GCM) patients have a history of autoimmune disorders. GCM cases are either fatal or require heart transplantation if not diagnosed early and treated with intensive immunosuppression.14

Previous viral infection may act as a trigger of post-infectious immune-mediated myocarditis. In addition to the previously most commonly detected enteroviruses, other viral genomes are identified in myocardial samples, most commonly parvovirus B19, Epstein–Barr virus, human herpesvirus 6, cytomegalovirus, and Herpes simplex viruses.4 The immune response to viral infections is considered to cause increased tissue damage. However, new data demonstrate that the sole presence of viral DNA/RNA with or without inflammation does not reflect the clinical outcome. It could be shown that the search for mRNA intermediates as a marker for transcriptional activity is crucial, as it predicts the adverse long-term outcome and is essential for deciding whether and how the patient should be treated.15 By understanding this pathophysiology, it is obvious that viral diagnostics in EMB is always required when inflammation is confirmed, as immunosuppressive treatment is contraindicated if a virus infection is present.6 Viruses can also trigger
secondary autoimmune mechanisms. For some viruses, it could be shown that viral persistence in the myocardium itself is associated with progressive deterioration of left ventricular ejection fraction, whereas the elimination of viral genomes led to a marked improvement in left ventricular function. In addition, the prevalence of cardiotropic viruses in myocardial tissue is probably much higher than expected in a diverse spectrum of heart failure conditions, including those not associated with a viral trigger or exacerbating role to date.

What is the most important lesson learned from the TIMIC study? First, a specific and causal treatment adapted to EMB-based pathophysiologically characterized cardiomyopathy forms leads to a significant clinical improvement and a better prognosis of the patients. Secondly, an individual and more differentiated selection of therapeutic candidates in MC/DCMi is required. The path to disease-specific, causal, and personalized treatment in MC/DCMi requires in-depth clinical, immunological, and virological phenotyping, including differential immune response testing with accurate immune cell typing, and identification of novel biomarkers (e.g., TLR3/TLR4, microRNA profiling, cytokine measurements, specific high titre autoantibody types, as well as gene expression profiling). This is the prerequisite for specific individualized immunosuppressive or antiviral treatment, future microRNA-based strategies, or targeted cytokine treatment. To address this clinical need, advanced diagnostics and guidelines are required, in order to optimize the management of this disease using a personalized treatment strategy.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References


