Treatment Options in Myocarditis

What We Know from Experimental Data and How It Translates to Clinical Trials

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Abstract
Although viral myocarditis has been mostly attributed to enterovirus and adenovirus infection until recently, the association with parvovirus B19 in Europe and hepatitis C virus in Asia has lately been noted. Clinical trials of antiviral agents, such as interferons, are in progress. Whereas immunosuppression with corticosteroids or cyclosporine is ineffective, immunosuppressors that do not promote viral replication, such as FTY720, are promising new approaches. The inhibition of nuclear factor-κB and angiotensin II effectively suppresses inflammation in experimental viral myocarditis.

In the EMCV animal model Pycnogenol inhibits viral replication, suppresses the expression of pro-inflammatory cytokines and mast cell-related mediators, and improves inflammation and myocardial necrosis. Pimobendan, FTY720 and Pycnogenol are promising agents for the treatment of viral myocarditis.

Schlüsselwörter: Myokarditis · EMC-Virus · Hepatitis C-Virus · Therapie

Zusammenfassung

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Treatment for Viral Myocarditis
The myocardium can be affected by a wide variety of viral infections. While myocarditis may be the primary disorder, it can also be a manifestation of systemic disease. When considering the viruses implicated in human myocarditis, one naturally focuses on group B coxsackieviruses, human enteroviruses that have been confirmed as primary causes of the disease for approximately 50 years. However, data from the mid-1990s suggest that two other viruses also play important pathogenic roles in this disease. Human adenovirus has been detected in a large number of cases of human myocarditis. Hepatitis C virus (HCV), a flavivirus, has also been identified as a potential cause of human myocarditis [1]. Cytomegalovirus, parovirus, herpesvirus, influenza virus, Epstein-Barr virus, and other viruses have been associated with viral myocarditis; however, there has been little direct evidence to demonstrate that these viruses cause myocarditis. The presence of viral antigens or nucleotides in the heart alone is not sufficient evidence to prove that the virus is the cause of myocarditis.

Among the main factors complicating the treatment strategies for viral myocarditis are the different therapeutic approaches to the disease. Treatment, for example with antivirals, could be beneficial in early stages, while other drugs, such as immunosuppressives, could be deleterious. In the later stages of viral myocarditis, for instance the autoimmune phase, therapies such as immunosuppressives may have a different effect.

The effect of treatment for viral myocarditis may depend on the virus. However, there have been few reports of clinical trials for virus-proven myocarditis.
This is because the diagnosis of viral myocarditis is often difficult, and the diagnostic methods of viral myocarditis have not been established or standardized. Therefore, the most important issues for the development of future therapy for viral myocarditis are to clarify viral etiology of myocarditis, to establish diagnostic methods, and to perform prospective clinical studies for virus-proven myocarditis.

We have developed a mouse model infected by the encephalomyocarditis virus (EMCV), in which a high incidence of severe myocarditis, congestive heart failure, and dilated cardiomyopathy is observed [2]. From this model, we have learned the natural history of EMCV-induced myocarditis. To clarify viral etiology of myocarditis and establish diagnostic methods, therapeutic, and preventive methods. Benefits of this animal are shown in Table 1.

### Antiviral Therapy with Interferons

In a murine model of myocarditis due to EMCV, human leukocyte interferon-(IFN-)α A/D inhibited the multiplication of virus in the heart and protected mice against myocarditis [3]. In an animal model of coxsackievirus myocarditis, human leukocyte IFN-α A/D administered 1 day prior to, or at the time of inoculation, inhibited viral multiplication in the heart and protected the mice against coxsackievirus B3 myocarditis.

Ribavirin (Rebetol®) is a synthetic nucleoside analog, structurally related to inosine and guanosine, which is broadly active against RNA and DNA viruses. Its efficacy has been clinically confirmed in measles, influenza and respiratory syncytial virus. Since the mode of action of IFN may differ from that of ribavirin, their possible synergism was studied. Plaque reduction assays in tissue cultures demonstrated a synergistic inhibition of EMCV replication by ribavirin and IFN-α A/D. A synergistic effect was also observed in vivo, which prolonged the survival of the animals, considerably decreased the myocardial virus titers, and significantly attenuated the inflammatory response and myocardial injury. A synergistic effect with IFN-α and ribavirin has also been demonstrated against coxsackievirus infection [4], and combined IFN-α and ribavirin has become the standard therapy in hepatitis C infection. This kind of drug combination may lower the incidence of adverse effects caused by either drug used alone in higher doses.

Therapeutic IFN-β has proven to be effective in a small number of patients with left ventricular dysfunction whose myocardial biopsy specimens were positive for enterovirus or adenovirus [5]. The author and colleagues from Shimane University, Japan, have studied the effects of IFNs on myocardial injury associated with active HCV-associated hepatitis. The thallium-201 single-photon emission computed tomography (201Tl SPECT) was used, since it is more sensitive than electrocardiography or echocardiography in detecting myocardial injury induced by HCV. The SPECT scores were reduced in eight of 15 patients (53%) whose treatment with IFNs was completed. Circulating HCV disappeared after INF therapy in all patients who had a decrease or no change in SPECT scores, whereas the HCV genomes persisted in the blood of two patients whose clinical status worsened [6]. This preliminary study suggests that INF is a promising treatment for myocardial disease caused by HCV. We have also reported treatment with INF, guided by serial measurements of serum HCV RNA and cardiac troponin T, in a patient presenting with dilated cardiomyopathy and striated myopathy due to HCV infection [7].

### Immunomodulatory Therapy

We conducted an earlier study to identify the effects of prednisolone in acute EMCV myocarditis in mice [8]. The survival of mice treated with prednisolone was significantly shorter than of the controls, and the neutralizing antibody titers in the prednisolone-treated group were significantly lower than in the controls. Similarly, mortality was significantly higher in mice with EMCV myocarditis treated with cyclosporine [9]. The mice in the actively treated group demonstrated a more severe degree of inflammation. When administered in the subacute stage, after the period of viral replication, cyclosporine caused a slight, although not significant increase in mortality, compared with untreated mice. Despite the absence of significant histological differences between treated and untreated mice, the cyclosporine-treated mice developed more severe heart failure.

Although its sample size was small and the study was preliminary, a trial of immunosuppression for active lymphocytic myocarditis associated with HCV

### Table 1. Benefits of the use of a murine model of EMCV myocarditis/heart failure.

| 1. Prediction of the long-term outcome of chronic heart failure patients by the effects of drugs on survival of mice at 14 days |
| 2. Histopathologic changes of the heart at day 7 |
| a) Myocardial necrosis |
| b) Cellular infiltration |
| 3. Measurement of comparable biomarkers of heart failure in humans |
| 4. Sequential analysis of hemodynamics |
| 5. Preventive effect of dilated cardiomyopathy at 3 months |
| 6. High reproducibility |
| 7. Safety: EMCV is not a human pathogen |