

CHAPTER

16

Treatment of Lymphocytic Myocarditis

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SUMMARY

How to treat lymphocytic myocarditis has changed in the last 50 years from a simple, unanswered clinical question to a highly complex, but still unanswered, clinical and basic research inquiry. The early literature, which preceded the now huge basic science exploration of myocarditis, speculated on its immunologic causes and the potential utility of steroid therapy.^{1,2} Clinical recognition of the many causes of myocarditis and fundamental basic research observations on disease mechanisms have led to a long list of potential therapies. Although only a few of them have been tested satisfactorily in clinical trials, therapies being considered are remarkably innovative and promising.

Therapy for lymphocytic myocarditis can be best understood if classified within broad categories of disease mechanisms (Table 16-1). Many of these therapies, especially those directed at autoimmunity, are as yet unproved, and, in fact, the disease mechanisms themselves are not fully understood. Much of the work on disease mechanisms has been done in animal models, which may not faithfully portray the disease as it occurs in humans or may represent a disease process that does not occur clinically. Thus, caution is required in translating experimental observations to the bedside.

MYOCARDITIS DUE TO ACTIVE INFECTION

VIRAL MYOCARDITIS

The term “viral myocarditis” has multiple meanings. It may refer to myocardial inflammation associated with active viral replication in the myocardium or to an autoimmune phase of myocarditis, which is thought to follow after active viral replication has ceased, or to both as a single, continuous disease entity. The term has become nearly synonymous with myocarditis because lymphocytic myocarditis, which is by far the most frequent form of myocarditis in most western and some eastern countries, is assumed, perhaps mistakenly, to be due to viral disease. To avoid confusion, it is prudent to reserve this term for active viral infection. “Postviral myocarditis” is an appropriate term for the autoimmune phase. When the origin is not clear, which is often the case in humans, “lymphocytic myocarditis” is the most appropriate term, because it describes the principal histologic finding without presuming a cause.

Viruses can infect the myocardium and induce heart failure and an interstitial inflammatory response during replication. This has been thoroughly delineated in animal models, and it has also been documented in humans by means of histologic examination and culture of myocardial biopsy specimens.

It is likely that most episodes of viral myocarditis spontaneously resolve without sequelae, as suggested by the high incidence of transient electrocardiographic changes that occur without associated heart failure during influenza epidemics. Thus, it appears that no

Table 16-1
Treatment of Lymphocytic Myocarditis

Etiology	Potential therapy
Infection	
Active virus	Direct antivirals, immune stimulation
Other	Direct antimicrobials
Postinfectious autoimmunity	Immune suppression, cytokine suppression
Autoimmunity	Immune suppression, cytokine suppression
Hypersensitivity	Withdrawal of agent, corticosteroids
Toxin	Withdrawal of agent, cytokine suppression, corticosteroids

therapy is needed in most cases of viral myocarditis, many or most of which go unrecognized. This recommendation must be tempered by the possibility that a proportion of cases of idiopathic dilated cardiomyopathy may result from remote or recent viral infection, as suggested by the late follow-up that Orinius³ undertook in patients with upper respiratory coxsackievirus infections and by the finding of presumed viral RNA and DNA in the myocardium of patients with idiopathic dilated cardiomyopathy.⁴⁻⁶ It is conceivable that if viral infection could be detected early in these cases, antiviral or other interventions might prevent subsequent development of idiopathic dilated cardiomyopathy.

Viral myocarditis would be expected to respond to direct antiviral chemotherapy. Enteroviruses (which include the coxsackieviruses) appear to account for the majority of cases in humans. Unfortunately, antivirals that specifically inhibit enteroviruses have not been tested adequately for clinical application. Specific inhibitors of influenza viruses (amantadine, rimantadine), herpesviruses (acyclovir, ganciclovir, foscarnet), and other non-human immunodeficiency viruses (ribavirin, lamivudine) now exist. In cases of myocarditis in which those viruses can be implicated, these drugs might be beneficial if administered during active viral infection. However, there is no proof of efficacy in humans as yet.

Nonspecific antiviral therapies have been tested or proposed for treatment of myocarditis. Immunoglobulin therapy, studied in children⁷ and in adults,⁸ appears promising, but it is not yet proved and may act against antibody-mediated autoimmunity rather than through viral suppression. Interferons also have the potential to ameliorate ongoing cardiotropic viral infections, but at present the only approved antiviral use is of interferon- α in condyloma acuminatum and hepatitis. A common myocyte membrane receptor for coxsackievirus and adenovirus has been proposed as a target for preventing development or spread of myocardial viral infection.⁹

Lymphocytic myocarditis is a well-recognized complication of acquired immunodeficiency syndrome (AIDS). Its incidence varies from less than 10% to more than 50%.¹⁰⁻¹³ Its etiology is debated. Human immunodeficiency virus myocardial infection, other coinfecting agents, or autoimmunity triggered by infection may be responsible. Because AIDS myocarditis is often associated with progressive dilated cardiomyopathy,¹¹ which is often lethal,¹⁴ early detection and therapy may improve outcome. In addition to conventional therapy, possibly including angiotensin-converting enzyme inhibitors, aggressive antiretroviral therapy might be helpful. Immunosuppressive therapy has also been reported anecdotally to improve congestive failure in patients with AIDS-related myocarditis, but this approach is as yet unproved.

OTHER INFECTIONS

Although viral and postviral myocarditis appear to be the most frequent types in highly developed countries, other infectious agents are common elsewhere. The myocarditis of Chagas disease and diphtheritic myocarditis are thought to be the most frequent of the myocarditides worldwide. Chagas myocarditis usually develops long after the acute infection with *Trypanosoma cruzi* and is largely immune mediated. Antiprotozoal therapy with nifurtimox or benznidazole may help. Diphtheritic myocarditis is common in epidemics. In an outbreak in Kyrgyzstan,¹⁵ 22% of patients with diphtheria developed myocarditis and the case-fatality rate was 3%. Diphtheria antitoxin combined with antibiotics (usually penicillin or erythromycin) is effective.

MYOCARDITIS DUE TO POSTINFECTIOUS AUTOIMMUNITY

The etiology of lymphocytic myocarditis in humans in developed countries is not clearly established. However, a good deal of circumstantial evidence points toward autoimmunity after viral infection as the major cause. Most cases of clinically suspected or biopsy-documented myocarditis in the United States fit into this category. Symptoms usually develop a few weeks after a viral infection. In the US Myocarditis Treatment Trial,¹⁶ 89% of enrollees had had signs or symptoms of a possible viral prodrome.

IMMUNOSUPPRESSIVE THERAPY

In deciding if patients with lymphocytic myocarditis should be treated for a presumed autoimmune disorder, the first step is to rule out active viral infection. In most patients this distinction is not difficult because they present afebrile days or weeks after a virus-like illness or report no such prodrome. In a small proportion the viral symptoms are more recent and fever is present. There are no randomized studies of therapy in patients with presumed

ongoing viral infection, but studies in mice demonstrate worsening of myocarditis when immunosuppression is instituted during the infectious phase.¹⁷ Except as a last resort, immunosuppression should be withheld in patients who have ongoing viral infection.

Another reason to withhold or delay immunosuppression in the early phase of myocarditis is that at least some components of the early immune response are beneficial and should not be suppressed. In the Myocarditis Treatment Trial,¹⁶ several indices of a heightened early immune response were associated with improved survival. One such relationship is illustrated in Figure 16-1, which shows reduced cumulative mortality in patients with higher concentrations of circulating cardiac IgG.

Efficacy of immunosuppression in the presumed autoimmune phase of lymphocytic myocarditis is not established. The Myocarditis Treatment Trial,¹⁶ which is the only completed randomized trial of therapy in myocarditis defined by generally accepted histologic criteria, showed improvement in left ventricular ejection fraction in patients receiving immunosuppression, but the extent of improvement was no better than that observed in subjects who did not receive immunosuppressive drugs (Fig. 16-2). Furthermore, survival in the 2 treatment limbs was identical (Fig. 16-3).

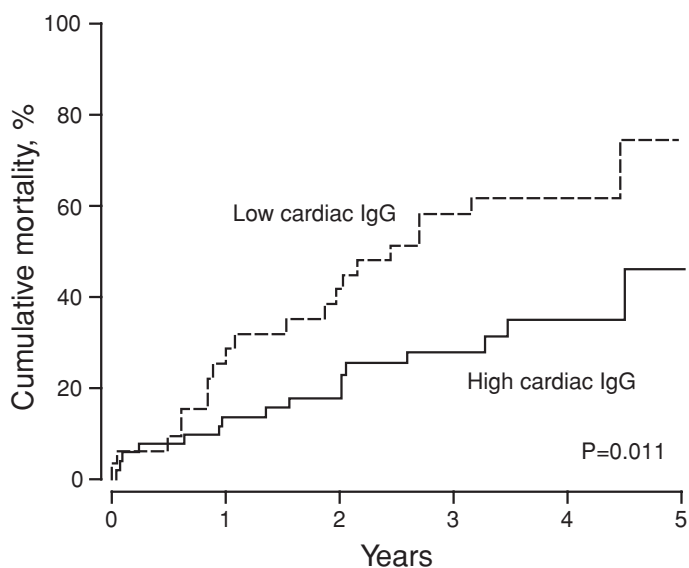


Fig. 16-1. In the US Myocarditis Treatment Trial, a high concentration of circulating cardiac-specific IgG was a univariate predictor of decreased mortality. It was not a significant predictor in a multivariate model. Nevertheless, this observation is consistent with beneficial effect of an early, appropriate immune response in myocarditis. (Modified from Mason JW. Immunopathogenesis and treatment of myocarditis: the United States Myocarditis Treatment Trial. *J Card Fail* 1996;2 Suppl 4:S173-S177. By permission of Elsevier Science.)

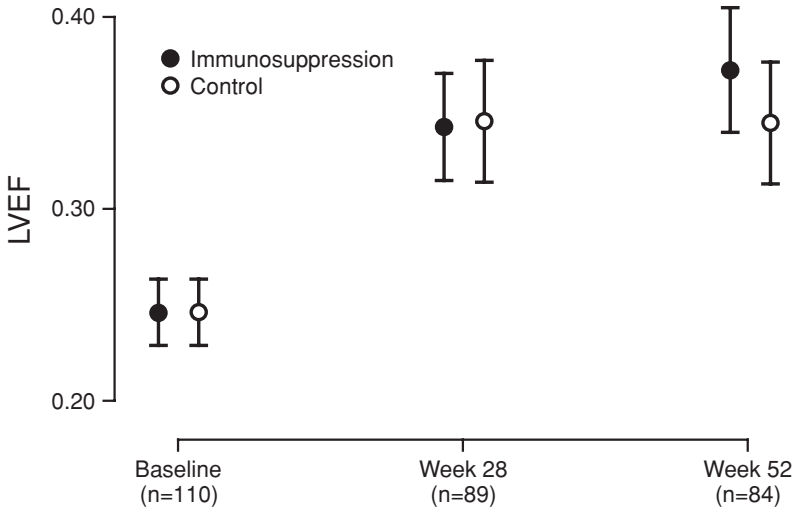


Fig. 16-2. In the US Myocarditis Treatment Trial, left ventricular ejection fraction (*LVEF*) increased significantly from baseline to week 28, and the increase was sustained to week 52. The extent of improvement was statistically equivalent in the immunosuppression and control groups. (From Mason et al.¹⁶ By permission of the Massachusetts Medical Society.)

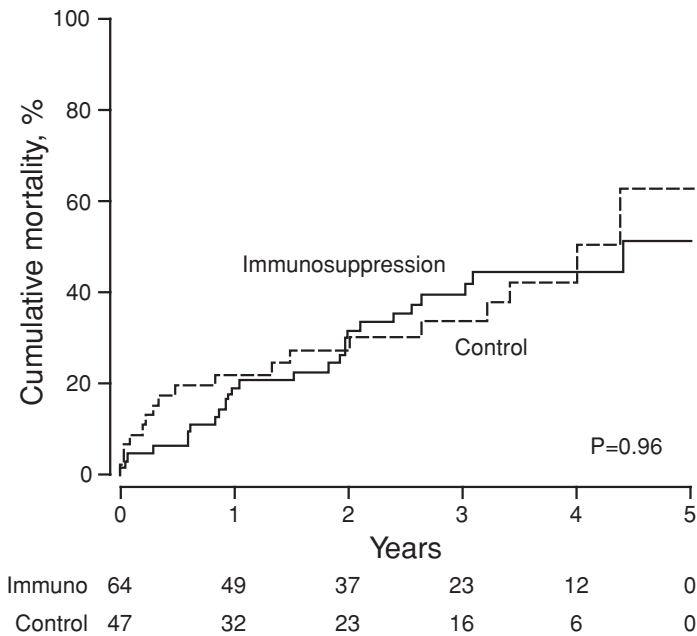


Fig. 16-3. There was no significant difference in mortality in the immunosuppression and control groups in the US Myocarditis Treatment Trial. The number of patients remaining in follow-up each year is displayed at the bottom of the graph. (From Mason et al.¹⁶ By permission of the Massachusetts Medical Society.)

Garg and colleagues¹⁸ performed a meta-analysis of 6 studies of immunosuppression in patients with myocarditis. They concluded that immunosuppression was not helpful. Reliability of this analysis is reduced by the fact that only 2 of the 6 studies were randomized controlled trials, and myocarditis was defined quite differently among the studies. In addition, all of the studies were relatively small, and each used a different form of immunosuppressive therapy.

The Myocarditis Treatment Trial remains the largest completed randomized trial of therapy for myocarditis. Nevertheless, the limits of its reliability should be understood. By design, the trial did not provide therapy tailored to specific causes of myocarditis, largely because specific therapies available today were not available at the time of the trial. The trial took place when there was an unusually prolonged cyclic reduction in the incidence of the most common cardiotropic virus infections. This accounts in part for the fact that it took 5 years to identify only 111 patients with biopsy-proven myocarditis in 31 enrollment centers. It may also account in part for the low incidence of biopsy specimens positive for myocarditis (only 10%) among the 2,233 patients suspected of having myocarditis. Thus, it is possible that the subjects enrolled in the trial had atypical causes of myocarditis. In addition, rigid adherence to the Dallas criteria¹⁹ for histologic diagnosis of myocarditis may have excluded some treatment-responsive patients. Finally, the trial did not attract many cases of fulminant myocarditis. These patients may have a better prognosis when immunosuppressed (and, perhaps, without immunosuppression).²⁰

Available information does not currently justify routine use of standard immunosuppressive therapy for lymphocytic myocarditis. However, a few exceptions seem appropriate. Immunosuppression should not be withheld as a potential life-saving measure in patients with cardiogenic shock who do not improve with conventional therapy. Patients without cardiogenic shock but who develop worsening heart failure are also candidates for a trial of immunosuppression. Patients who apparently responded to previous immunosuppressive therapy and develop recurrent myocarditis may be immunosuppressed again, and consideration should be given to use of different agents, larger doses, or a longer period of therapy.

Cardiopulmonary support has been used successfully in cases of cardiogenic shock due to acute and fulminant myocarditis. Kato et al.²¹ reported on 9 patients with biopsy-confirmed myocarditis and cardiogenic shock treated with percutaneous cardiopulmonary support. All 9 patients improved hemodynamically and were weaned from the support device. Two patients died at days 13 and 113 of multiorgan failure and pneumonia. The remaining 7 were alive at a mean follow-up of 34 months. Kawahito and colleagues²² reported on 6 patients who presented with cardiogenic shock 2 to 7 days after flu-like symptoms. The ejection fractions ranged from 15% to 30%. Five patients (83%) were weaned from support and dismissed. Ventricular-assist devices were used successfully as a bridge to transplantation in patients with lymphocytic myocarditis,²³ nonspecific myocarditis,²⁴ and giant cell myocarditis.²⁵

Another category of patients with myocarditis in whom immunosuppression should be considered is the group presenting with life-threatening ventricular arrhythmias. Because myocarditis is often a self-limited process, in most cases it should be possible to avoid aggressive antiarrhythmic measures, such as ablation and cardioverter-defibrillator implantation, which are usually used for long-term suppression of arrhythmias. If a patient with myocarditis is facing the possibilities of those therapies, an attempt first to eliminate the arrhythmia by suppressing the inflammatory process is appropriate in some cases.

OTHER THERAPIES

The ongoing European Study of Epidemiology and Treatment of Cardiac Inflammatory Disease is a multicenter therapy trial based in Germany in which a recognition of the multiple etiologies of lymphocytic myocarditis is incorporated into the randomized treatment algorithm. Patients with evidence of active cytomegalovirus infection receive hyperimmune globulin, and if that is not effective, ganciclovir. Patients who have biopsy specimens containing enteroviral genomic material detected by polymerase chain reaction receive interferon- α . All others receive corticosteroids and azathioprine. None of these therapies are proven to be effective. The hope is that tailored therapy will be more likely to be successful.

Numerous new therapies have been proposed for treatment of lymphocytic myocarditis due to postinfectious autoimmunity (Table 16-2). Most of these new therapies are immunomodulatory. They attempt to suppress the evolution of the autoimmune process at an early stage (eg, FTY720), block immune mediators such as the cytokines (eg, anti-tumor necrosis factor- α antibodies), attack a specific molecular mechanism (T-cell antigen receptor-based DNA vaccines), or remove immune mediators from the circulation (eg, immunoabsorption). Other potential new therapies are derived from demonstrated success in prevention of adverse remodeling in congestive heart failure (eg, inhibition of angiotensin-converting enzyme). None of these new therapies were tested adequately in humans. Nevertheless, they represent the future in management of myocarditis and provide a reason for genuine optimism.

NONINFECTIOUS AUTOIMMUNE MYOCARDITIS

Autoimmune myocarditis also occurs independently of infectious insults. Immunoglobulin infiltration alone or in combination with cellular infiltration of the myocardium has been identified in several collagen vascular disorders, including rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa, dermatomyositis and polymyositis, scleroderma, and the CREST (calcinosis cutis, Raynaud phenomenon, esophageal dysfunction, sclero-

Table 16-2
New Therapies for Myocarditis Due to Postinfectious Autoimmunity

Therapy	Reference	Status
Intravenous immunoglobulins	7,8	Uncontrolled trials in humans suggest efficacy
IgG adsorption	26	Effective in case-control studies in humans with idiopathic dilated cardiomyopathy
Anti-tumor-necrosis factor- α antibody	27	Effective as early therapy in mice
Nitric oxide inhibition	28	Pimobendan efficacy in mice may be mediated by inhibition of inducible nitric oxide synthase
T-cell antigen receptor-based DNA vaccines	29	Effective in murine autoimmune carditis
Tacrolimus	30-32	Effective in various murine models
FTY720	33	Reduces inflammatory infiltration in rats when administered early
Vesnarinone	34	Improves survival and reduces myocardial damage in mice by inhibiting natural killer cell activity
β -Adrenergic receptor blockers	35-37	Metoprolol is ineffective but carteolol is effective in improving CHF in murine models, a β_1 -agonist is beneficial, no human studies
Calcium channel blockers	38	Amlodipine appears to be the most effective calcium antagonist in experimental models
α -Adrenergic receptor blockers	39	Helpful as early and protracted therapy
Angiotensin-converting enzyme inhibitors	40	Enzyme inhibitors and receptor blockers reduce myocardial injury in experimental myocarditis
Mu-Fang-Ji-Tang	41	Chinese herbal medicine improves CHF in murine myocarditis

CHF, congestive heart failure.

dactly, and telangiectasia) syndrome.⁴² There are no large series or controlled trials of therapy for myocarditis in these conditions. However, anecdotal experience showed that myocarditis is more likely to occur during heightened disease activity and to respond to the same therapies used to reduce that activity. Corticosteroids produce rapid and extensive improvement of ventricular function in some cases.

Numerous other disease-associated myocarditides are recognized, such as those associated with acute rheumatic fever and Kawasaki disease. Other disease-independent types of myocarditis, such as Dressler syndrome and postcardiotomy syndrome, are thought to have an autoimmune etiology. Any cardiac injury that releases myocellular proteins may be capable of inducing autoimmune carditis. Myosin is especially strongly implicated as a cause of autoimmune myocarditis.^{43,44} In most of these conditions, corticosteroids and other immunosuppressive therapies acutely improve ventricular dysfunction, but long-term outcomes have not been studied adequately.

MYOCARDITIS DUE TO TOXINS

Numerous drugs and chemicals cause myocarditis. In some cases, these agents directly damage myocytes. Leak of intracellular contents into the interstitium induces inflammation and may also initiate a secondary autoimmune process. Other mechanisms undoubtedly exist. A hypersensitivity response to drugs and chemicals can be distinguished from direct toxicity by the presence of eosinophils. In either case, the most effective treatment is removal of the offending agent. Addition of corticosteroids may help when inflammation is unusually severe, ventricular dysfunction is markedly depressed, or recovery is delayed.

SUMMARY

Because lymphocytic myocarditis has multiple etiologies, therapy should be individualized according to the specific etiology. Unfortunately, efficacy of most therapies used or proposed for use in lymphocytic myocarditis has not been proven. Until this proof is available, specific and nonspecific antiviral measures should be considered for use in those relatively few patients who present with documented ongoing viral infection. Likewise, appropriate antimicrobial therapy is always indicated in lymphocytic myocarditis caused by bacterial and other organisms. The area of greatest controversy is the use of immunosuppressive and other immunomodulatory therapies for noninfectious and postinfectious myocarditis. Although this approach is unnecessary in many cases and ineffective in others, there are specific circumstances in which immunosuppression should be undertaken.

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