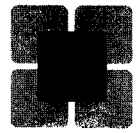

Lymphocytic myocarditis and dilated cardiomyopathy: treatment with immunosuppressive agents

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■ Thirty-four patients with history of congestive heart failure, dilated cardiomyopathy, and biopsy-proven lymphocytic myocarditis were treated for six months with immunosuppressive agents (prednisone and azathioprine) in addition to standard therapy for congestive heart failure. Seventy-three percent had improvement or resolution of the lymphocytic infiltrate, whereas 27% had persistent infiltrates. Improvement in myocardial histologic findings was unpredictable and did not correlate with age, gender, duration of symptoms, initial functional class, severity of left ventricular dysfunction, intensity of initial inflammatory infiltrate, or degree of myocardial cell injury. Histologic response was associated with significant improvement in left ventricular ejection fraction, but not cardiothoracic ratio, left ventricular dimensions, or survival. Functional class improved equally whether patients' disease did or did not respond to the treatment, and was not necessarily associated with objective improvement in cardiac function. Immunosuppressive therapy resulted in serious or fatal side effects in 24% of patients. Overall long-term survival was 79% at one year and 76% at two years. Poor survival was related to left ventricular ejection fraction less than 20%, male sex, age <50 years, and marked left ventricular dilation, but not to myocardial histologic findings. These findings indicate that the potential benefits *v* the risks of immunosuppressive therapy must be weighed carefully in the individual patient.

□INDEX TERMS: CARDIOMYOPATHY, CONGESTIVE; IMMUNOSUPPRESSIVE AGENTS; MYOCARDITIS □CLEVE CLIN J MED 1989; 56:628–635

LYMPHOCYTIC myocarditis is an ill-defined disease of uncertain etiology characterized by an infiltration of lymphocytes in the myocardium and myocardial cell injury.[1] Based on animal data, some cases of myocarditis are thought to be related directly to a viral invasion of the myocardium, most commonly by a coxsackievirus.[2] The virus usually is eradicated within days after the onset of infection by macrophages and humoral antibodies.[3] However, the infecting virus may produce a neoantigen in the myocardium, which in turn activates the cellular immune system.[4] Cytotoxic T lymphocytes form an infiltrate in the myocardium and may persist for an indefinite period, perhaps as a result of defective lymphocyte suppressor cell function or other unknown factors.[5,6] This ongoing

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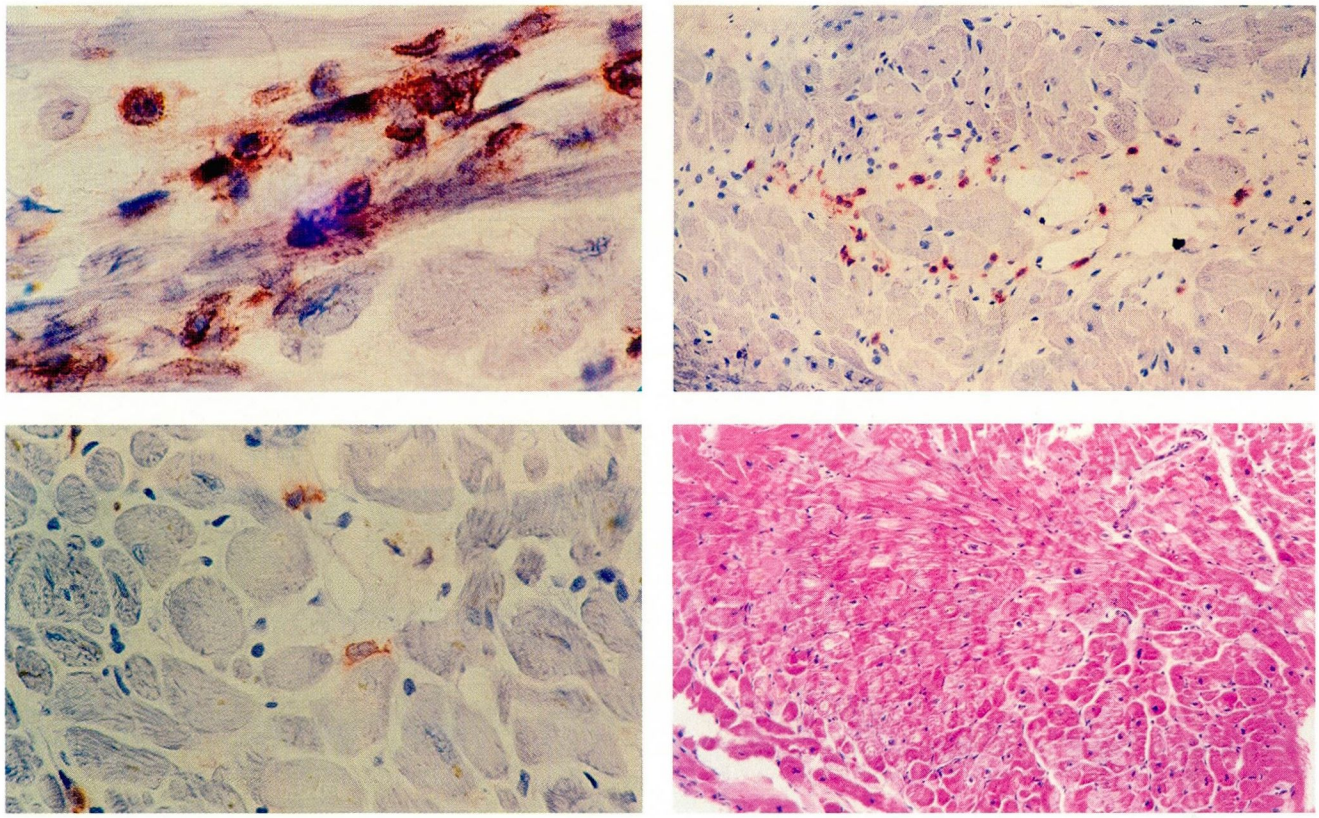

A, B
C, D

FIGURE 1A. Acute lymphocytic myocarditis, immunoperoxidase reaction for T lymphocytes. The red granules of reaction product can be seen surrounding the nuclei of individual T lymphocytes. The nuclei and myocytes are stained pale blue with hematoxylin counter stain. (×425) FIGURE 1B. Persistent lymphocytic myocarditis, immunoperoxidase reaction for T lymphocytes, at low magnification. A diffuse infiltrate of T lymphocytes is present in the center of the photograph, surrounding a cluster of myocytes. The red immunoperoxidase reaction product surrounds the nuclei of individual T lymphocytes. The counter stain is hematoxylin. (×125) FIGURE 1C. Resolving lymphocytic myocarditis, immunoperoxidase reaction for T lymphocytes. The number of T lymphocytes is notably diminished from *Figures 1A* and *1B*. (×160) FIGURE 1D. Resolved lymphocytic myocarditis. The normal myocardium is illustrated in this photomicrograph following resolution of lymphocytic myocarditis. Hematoxylin and eosin stain. (×125)

cell-mediated inflammatory response may cause progressive myocardial cell injury, eventually leading to dilated cardiomyopathy.[7,8]

Myocarditis has been treated with immunosuppressive agents in an attempt to prevent the development of dilated cardiomyopathy.[9–17] Previous reports of therapy have been inconclusive because they involved uncontrolled treatment strategies in small numbers of patients. Circumstantial evidence still exists, however, that immunosuppressive therapy may be effective in eradicating the inflammatory response. Currently, a multicenter myocarditis treatment trial is enrolling small numbers of patients, but the results of this study will not be available for several years.

In the meantime, physicians continue to treat myocarditis without knowing the anticipated outcome of histologic and clinical response. This report, which summarizes a three-year experience treating patients with lymphocytic myocarditis, dilated cardiomyopathy, and congestive heart failure, provides guidelines for clinicians wishing to use this treatment strategy.

MATERIALS AND METHODS

The study group consisted of 34 consecutive patients with dilated cardiomyopathy, a history of congestive heart failure, and biopsy-proven lymphocytic myocarditis. These patients represented 21% of patients with dilated cardiomyopathy and congestive heart failure undergoing myocardial biopsy at The Cleveland Clinic

A, B

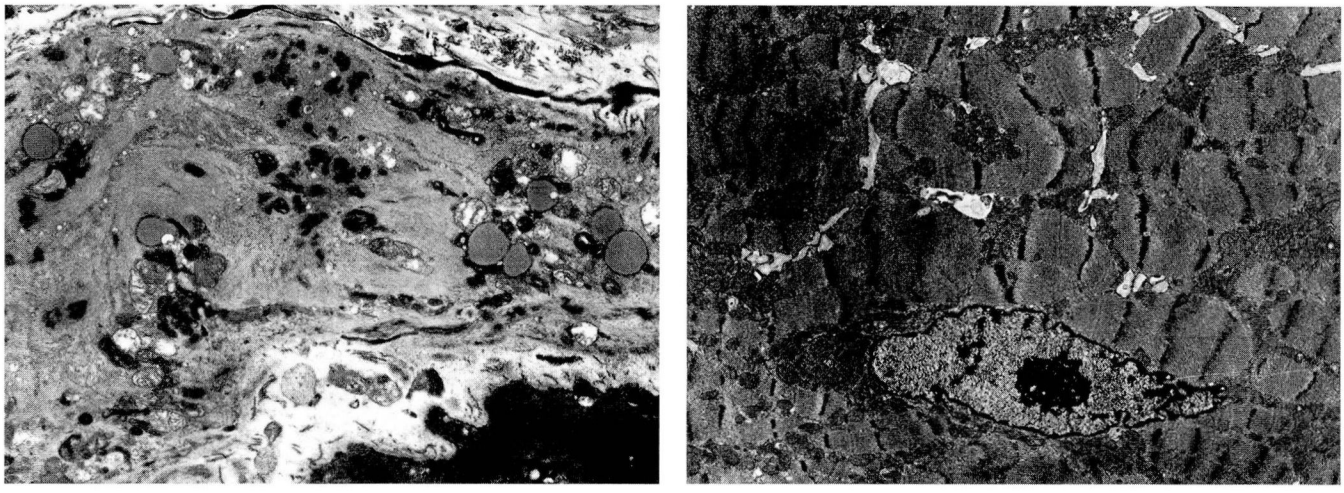

FIGURE 2A. Cell injury in lymphocytic myocarditis. In our experience, the only reliable way to identify cell injury in myocarditis is by electron microscopy. The injured cell exhibits accumulation of lipid droplets and loss of all normal sarcomeric structures. Z lines and myosin filaments have disappeared, leaving only actin filaments and abnormal aggregates of Z-band material. Note that the cell and the mitochondria are not swollen, and the sarcolemma is intact, indicating that this injury is reversible. Stained with lead citrate and uranyl acetate. (×8600) FIGURE 2B. Electron micrograph of normal myocardium from an endomyocardial biopsy specimen. This figure is presented for a comparison with *Figure 2A*. The sarcomeres are of differing widths, indicating variable degrees of contraction, a normal finding in biopsy specimens. All of the normal features of sarcomeres can be identified. Stained with uranyl acetate and lead citrate. (×7100)

Foundation during a three-year period. Patients with coronary artery disease, primary valvular heart disease, hypertensive heart disease, and congenital heart disease were excluded from the study. The patients' conditions were stabilized with conventional therapy for congestive heart failure, including digitalis, diuretics, vasodilators, warfarin, and antiarrhythmic agents, prior to immunosuppressive therapy. The doses of drugs for congestive heart failure remained constant in most patients during the immunosuppressive treatment phase.

Baseline assessment included history and physical examination, routine laboratory blood studies, electrocardiography (ECG), chest radiograph, 24-hour cardiac monitoring, two-dimensional echocardiogram, radionuclide left ventricular ejection fraction, right- and left-sided heart catheterization, and transvenous right ventricular endomyocardial biopsy.

Endomyocardial biopsies were performed with a 9-F Stanford bioptome inserted via the right internal jugular vein. Three to six samples were obtained from the right ventricular septum. The biopsy specimens were divided into three groups. The first group was fixed in B5, embedded in paraffin, sectioned, and stained for light microscopy with hematoxylin and eosin, Movat's pentachrome, Masson's trichrome, and sulfated alcian blue. The second portion was rapidly frozen in isopentane and cooled in liquid nitrogen. Immunohistochemical studies were performed on frozen sections with an indirect immunoperoxidase technique utilizing monoclonal antibodies as T cell, B cell, and macrophage markers. A third portion was fixed in glutaraldehyde, post-fixed in osmium tetroxide, and embedded in an epoxy resin. One-micrometer plastic sections were stained with a mixture of basic fuchsin and toluidine blue for high-resolution light microscopy. A minimum of two blocks from each patient was selected for electron microscopic examination. Thin sections were doubled-stained with uranyl acetate and lead citrate, examined, and photographed using a Philips 400 or 410 electron microscope.[18]

The myocardial biopsies were read by two or more pathologists who did not know the clinical diagnosis (*Figures 1* and *2*). The entire biopsy specimen was examined, and each high-power field was counted. Myocarditis was defined as the presence of five or more T lymphocytes per high-power field plus evidence of myocardial cell injury documented by electron microscopy, or 10 or more T lymphocytes per high-power field with or without myocardial cell injury (*Figures 1A* and *2A*). Persistent myocarditis was defined as an infiltrate similar to or worse than the initial biopsy specimen (*Figure 1B*). Resolving myocarditis was defined as an infiltrate less

TABLE 1
COMPARISON OF BASELINE PATIENT DATA WITH RESPONDERS AND NONRESPONDERS

	Total Patients (*N* = 34)	Responders (*N* = 24)*	Nonresponders (*N* = 9)*	*P* value
Age	49.0 ± 12.1 yr	47.5 ± 11.4 yr	53.4 ± 13.9 yr	0.22
Gender	24 males (70.6%)	17 males (70.8%)	6 males (66.7%)	0.99
Viral illness	6 pts (18.2%)	5 pts (20.8%)	1 pt (11.1%)	0.99
Symptoms (months)	4.8 ± 4.3 months	4.1 ± 4.2 months	7.0 ± 4.2 months	0.08
Ethanol excess†	12 pts (36.4%)	10 pts (41.7%)	2 pts (22.2%)	0.43
Sedimentation rate	15.2 ± 13.2 mm/h	15.1 ± 14.2 mm/h	16.0 ± 4.2 mm/h	0.95
Cardiothoracic ratio	0.56 ± 0.07	0.55 ± 0.08	0.58 ± 0.06	0.22
Echo (LVEDD)	69.4 ± 11.7 mm	69.1 ± 11.1 mm	70.3 ± 14.7 mm	0.82
LV ejection fraction	25.5 ± 8.7%	25.2 ± 9.2%	26.0 ± 8.1%	0.81
Ventricular tachycardial‡	17 pts (50%)	12 pts (50%)	4 pts (44.4%)	0.99
T lymphocytes/HPF	16.5 ± 11.6	18.8 ± 12.4	11.9 ± 7.6	0.13
Severe myocyte injury	20 pts (55.8%)	13 pts (54.2%)	7 pts (77.8%)	0.26

* 1 patient died prior to second biopsy.
† More than 3 drinks/day.
‡ Nonsustained or sustained.
LV = left ventricle; *LVEDD* = left ventricular end-diastolic diameter.

severe than on the original biopsy specimen with evidence of reparative changes (*Figure 1C*). Resolved myocarditis was defined as the absence of an inflammatory infiltrate and no evidence of myocardial cell injury (*Figure 1D*). Mild myocardial cell injury included intracellular changes of increased glycogen and mitrochondria but without demonstrable changes in the contractile apparatus. Severe myocardial cell injury involved loss of specific contractile elements (generally Z lines and myosin filaments) (*Figure 2*). A control group consisted of endomyocardial biospy specimens obtained from normal donor hearts at the time of cardiac transplantation. The control biopsy specimens contained less than 1 T lymphocyte (range 0–2) per high-power field, which was similar to values obtained by other investigators.[19–23] The definitions of myocardial cell injury were based on previous biopsy studies in patients with cardiac transplant rejection.[24]

All patients were treated with prednisone and azathioprine. Prednisone was initiated at 1 mg/kg/day in divided oral doses and tapered over the next two months to a maintenance dose of 0.3 mg/kg/day. Azathioprine was administered orally at 2 mg/kg/day for six months. The dose of azathioprine was reduced if the white blood cell count was less than 3,500/mm^3. Patients were reevaluated at 2, 5, and 7 months. History and physical examination, ECG, radionuclide left ventricular ejection fraction, echocardiogram, and endomyocardial biopsy were repeated at these times. Follow-up data on all patients were obtained up to 34 months after initiation of treatment.

Tests for mean differences were performed with the two-tailed Student *t* test. Two-way tables were developed for categorical variables, and chi-square analysis or Fisher's exact test was used to test for independence. Patient survival curves were constructed using Kaplan-Meier estimates. Univariate comparison among curves was performed with the log rank test.

RESULTS

Thirty-four patients (24 men, 10 women) were entered into the study. Age ranged from 26 to 69 years (mean, 49.0 years). Seven patients (21%) had a history of viral illness prior to onset of symptoms. Duration of symptoms prior to biopsy was 0.25 to 18 months (mean 4.8 months). Seventeen patients (50%) had documented nonsustained or sustained ventricular tachycardia. Thirteen patients (38%) had a history of at least moderate alcohol ingestion. Westergren sedimentation rate was elevated in four patients (12%). Fourteen patients (41%) were New York Heart Association functional class IV, 10 patients (29%) were functional class III, nine patients (26%) were functional class II, and one patient (3%) was functional class I. All patients had abnormal ECGs, most commonly left bundle branch block, and most patients had a cardiothoracic ratio greater than 0.5 on the initial chest radiograph. Left-ventricular end-diastolic dimensions by echocardiography ranged from 45 to 86 mm (mean, 69 mm). The mean left ventricular ejection fraction prior to treatment was 25.5%. The initial biopsy specimens revealed a mean of 16.5 T lymphocytes per high-power field and

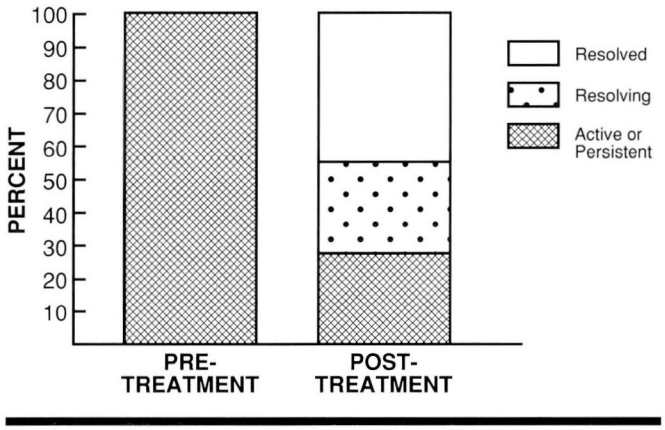

FIGURE 3. Percent of patients with resolved, resolving, or persistent myocarditis after immunosuppressive therapy.

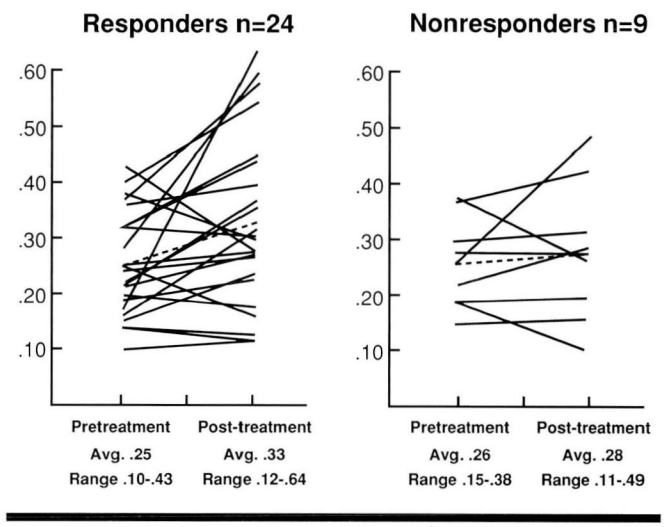

FIGURE 4. Radionuclide left ventricular ejection fraction (pre- and posttreatment) in patients with and without histological response. Ejection fraction was significantly improved (mean 8%) in responders (P=.009) as compared with an insignificant change (mean 2%) in nonresponders (P=.49).

severe myocardial cell injury in 20 patients (59%) (*Table 1*).

The patients were divided into two groups based on histologic response. Twenty-four patients (73%) had improvement or complete resolution of the infiltrate during the course of therapy (responders). Of these, 18 cases resolved and six improved (*Figure 3*). Histological response occurred slowly over several months in this group. Nine patients (27%) had infiltrates that persisted despite treatment (nonresponders). One patient died suddenly three weeks into the study prior to the second biospy. Histologic response could not be predicted by age, gender, viral prodrome, duration of symptoms, arrhythmias, heart size, radionuclide ejection fraction, severity of inflammatory infiltrate, or degree of myocardial cell injury (*Table 1*).

Improvement in histologic findings was associated with an increase in left ventricular ejection fraction (*Figure 4*) (P=.009) but not a reduction in cardiothoracic ratio or left ventricular dimensions. In nonresponders, left ventricular ejection fraction, cardiothoracic ratio, and left ventricular end-diastolic dimensions did not change significantly after treatment.

Functional class improved similarly in both groups (71% in responders *v* 67% in nonresponders) (*Figure 5*). Improvement in functional class did not correlate with improved histologic findings, improved left ventricular ejection fraction, smaller heart size, or reduction of left ventricular dimensions (*Table 2*).

Follow-up data were obtained on all patients up to 34 months after initiation of treatment (mean 18 months). Two patients (6%) experienced histologic relapse after immunosuppressive therapy was discontinued. Actuarial survival for all patients was 79% at one year and 76% at two years (*Figure 6*). Two patients (nonresponders) with severe left ventricular dysfunction underwent cardiac transplantation at 13 months and 17 months, respec-

TABLE 2
RELATIONSHIP BETWEEN POST-TREATMENT FUNCTIONAL CLASS AND MYOCARDIAL HISTOLOGY, HEART SIZE, AND EJECTION FRACTION

	NYHA FUNCTIONAL CLASS		
	Improvement*	No change/worse	*P* value
Improved histology			
Yes = 24 (72.7%)	17 (73.9%)	7 (70.0%)	
No = 9 (27.3%)	6 (26.1%)	3 (30.0%)	0.99
Decreased heart size†			
Yes = 8 (26.7%)	7 (30.4%)	1 (14.3%)	
No = 22 (73.3%)	16 (69.6%)	6 (85.7%)	0.64
Decreased LV dimensions‡			
Yes = 4 (21.1%)	3 (25.0%)	1 (14.3%)	
No = 15 (78.9%)	9 (75.0%)	6 (85.7%)	0.99
Improved LVEF§			
Yes = 15 (45.5%)	12 (52.2%)	3 (30.0%)	
No = 18 (54.5%)	11 (47.8%)	7 (70.0%)	0.28

* At least one functional class.
† ≥ 6% reduction of cardiothoracic ratio.
‡ ≥ 10% reduction of LV end-diastolic dimensions on echocardiogram.
§ > 5% improvement of radionuclide left ventricular ejection fraction.
NYHA = New York Heart Association; *LV* = left ventricle.

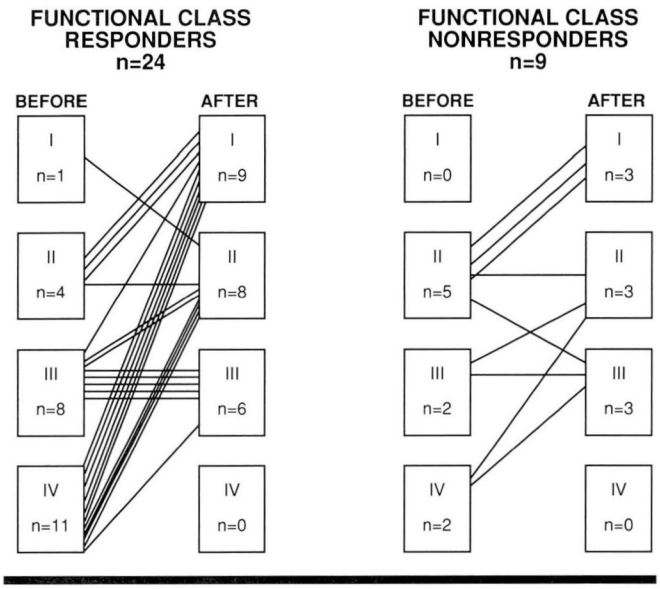

FIGURE 5. Comparison of functional class (pre- and posttreatment) in patients with and without histological response. The two groups improved to similar degrees ($P=.99$).

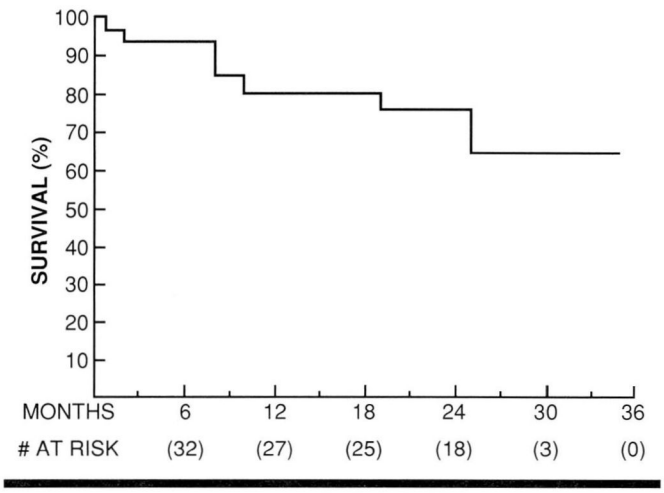

FIGURE 6. Overall survival curve in patients with myocarditis and dilated cardiomyopathy. One-year survival was 79% and two-year survival was 76%.

tively. Poor survival was related to male sex ($P=.02$), age less than 50 years ($P=.05$), left ventricular ejection fraction less than 20% ($P=.04$), and left ventricular end-diastolic diameter greater than 65 mm ($P=.04$), but not viral prodrome, duration of symptoms, functional class, cardiac arrhythmias, or histologic response (*Table 3*).

Side effects from immunosuppressive therapy were common. Most patients developed cushingoid body habitus from steroids. Three patients (9%) developed hyperglycemia requiring therapy with insulin or oral hypoglycemic agents. Two patients (6%) developed gastric ulcers and one required multiple blood transfusions for gastrointestinal bleeding. Another patient developed staphylococcal skin infection that required hospitalization and systemic antibiotic therapy. Immunosuppressive therapy was withdrawn in one patient at two months following a normal biopsy because reactive depression impaired compliance with the drug regimen. In another patient, azathioprine was discontinued after two weeks because of progressively abnormal liver function tests and jaundice. Two patients died during the treatment phase of the study. One patient with known ventricular arrhythmias died suddenly three weeks after entry into the study. One diabetic patient developed *Pneumocystis carinii* pneumonia and died two months after initiation of immunosuppressive therapy.

DISCUSSION

Diagnosis of myocarditis is difficult, and treatment with immunosuppressive agents is controversial.[25] In this study, most cases of myocarditis could not be diagnosed accurately by clinical criteria (febrile illness, elevated sedimentation rate, abnormal white blood cell count, acute ECG changes). Since most patients presented with dilated cardiomyopathy and congestive heart failure only, the diagnosis of myocarditis required endomyocardial biopsy for substantiation.

More than one third of the patients had consumed at least a moderate amount of alcohol on a daily basis in the past. Some of these patients were thought to have alcoholic cardiomyopathy but were later found to have biopsy-proven myocarditis. Whether alcohol has a role in the pathogenesis of myocarditis is uncertain. However, a history of alcohol ingestion does not exclude underlying myocarditis as the etiology for dilated cardiomyopathy and congestive heart failure. The clinical course for this group of patients was similar to that for the other patients in the study.

Pathologic examination of biopsy specimens utilized immunohistochemistry to define and quantitate T lymphocytes, and electron microscopy to delineate myocyte injury. Histologic diagnosis of myocarditis based on the Dallas criteria relies entirely on qualitative interpretation of the light microscopy of paraffin sections.[2,26,27] We have previously shown that the evaluation of myo-

cardial cell injury in such preparations is not reliable.[18-24] Lie[25] recently noted the problems with the Dallas classification, including high interobserver variability when the same biopsy specimens were independently examined by a select group of pathologists, many of whom served on the panel that established the Dallas criteria. Therefore, we elected to base our histologic evaluation on the quantitative number of T lymphocytes per high-power field marked by monoclonal antibodies in frozen sections, and on the electron microscopic evaluation of myocardial cell injury.

It was not possible to predict which patients with myocarditis would respond to immunosuppressive therapy. Other indexes (clinical or histologic) that might accurately predict the response to immunosuppressive therapy must be identified. The majority of patients treated with prednisone and azathioprine experienced a resolution or improvement of the inflammatory infiltrate. Whether histologic improvement was directly related to these agents or occurred spontaneously could not be determined.

Both groups of patients (responders and nonresponders) experienced an improvement in overall functional class. This improvement was not necessarily associated with objective improvement in heart size or ejection fraction. We suspect that functional improvement was a result of careful medical management of heart failure rather than immunosuppressive agents.

Two patients (6%) experienced relapse after immunosuppressive therapy was discontinued. Relapse has been reported in 5% to 10% of patients in other studies.[9] The efficacy of long-term immunosuppressive therapy in patients with relapse or persistent infiltrates requires further investigation.

Treatment with immunosuppressive drugs is not without hazard. The majority of patients experienced minor side effects from prednisone but few had adverse effects from azathioprine. Eight patients (24%) experienced serious side effects and one of them died secondary to opportunistic pulmonary infection. Other immunosuppressive agents, such as cyclosporine, have their own unique side effects, but the efficacy of these agents remains unproven. The multicenter myocarditis treatment trial may provide more information.[28]

Survival was not better in patients with histological improvement than in patients having persistent infiltrates. Prognostic indicators of poor survival were age less than 50 years, male sex, low left ventricular ejection fraction, and markedly dilated left ventricular chamber size.

In summary, this study demonstrates that immunosuppressive therapy with prednisone and azathioprine is associated with improvement or resolution of the inflammatory infiltrate in most patients. Histologic response is unpredictable, and indexes to predict response must be identified in the future. Left ventricular ejection fraction significantly increases with histological response. Improvement in functional class is related to careful medical management rather than histological response. Side effects of immunosuppressive drugs are common and occasionally life-threatening. Survival is not influenced by histologic response to immunosuppressive agents. Therefore, the potential benefit *v* risks of immunosuppressive therapy must be weighed carefully in the individual patient.

TABLE 3
PROGNOSTIC INDICATORS OF SURVIVAL

	Cumulative Survival		Log rank test
	1 Year	2 Years	*P* value
Overall patients (*N* = 34)	27 (79.4%)	9 (75.6%)	—
Age			
≤ 50 Years (*N* = 17)	11 (64.7%)	4 (56.6%)	
> 50 Years (*N* = 17)	16 (94.1%)	5 (94.1%)	0.05
Gender			
Male (*N* = 24)	17 (70.8%)	4 (64.9%)	
Female (*N* = 10)	10 (100%)	5 (100%)	0.02
Viral illness			
Yes = 7	4 (57.1%)	4 (57.1%)	
No = 27	23 (85.2%)	5 (80.2%)	0.08
Duration of symptoms			
≤ 3 months (*N* = 19)	16 (84.2%)	6 (84.2%)	
> 3 months (*N* = 15)	11 (73.3%)	3 (62.9%)	0.37
Post-treatment functional class			
I (*N* = 12)	12 (100%)	6 (92.3%)	
II (*N* = 11)	8 (72.7%)	2 (72.7%)	
III (*N* = 9)	7 (77.8%)	1 (62.2%)	0.33
Ventricular arrhythmias			
Yes = 17	14 (82.4%)	4 (74.1%)	
No = 17	13 (76.5%)	5 (76.5%)	0.77
LVEDD			
< 65 mm (*N* = 10)	10 (100%)	3 (100%)	
≥ 65 mm (*N* = 15)	11 (73.3%)	1 (62.9%)	0.04
Post-treatment LVEF			
≤ 20% (*N* = 7)	5 (71.4%)	2 (47.6%)	
20–30% (*N* = 11)	10 (90.9%)	2 (90.9%)	
> 30% (*N* = 14)	12 (85.7%)	6 (85.7%)	0.04
Severity of infiltrate			
≤ 15 Lymphocytes* (*N* = 24)	18 (75.0%)	4 (75.0%)	
> 15 Lymphocytes* (*N* = 10)	9 (90.0%)	5 (78.9%)	0.40
Histological response			
Yes = 24	20 (83.3%)	8 (79.0%)	
No = 9	9 (77.8%)	1 (77.8%)	0.86

* T lymphocytes per high power field.
LVEF = left ventricular ejection fraction; *LVEDD* = left ventricular end-diastolic dimensions on echocardiogram.

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