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## A CLINICAL TRIAL OF IMMUNOSUPPRESSIVE THERAPY FOR MYOCARDITIS

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**Abstract** *Background.* Myocarditis is a serious disorder, and treatment options are limited. This trial was designed to determine whether immunosuppressive therapy improves left ventricular function in patients with myocarditis.

*Methods.* We randomly assigned 111 patients with a histopathological diagnosis of myocarditis and a left ventricular ejection fraction of less than 0.45 to receive conventional therapy alone or combined with a 24-week regimen of immunosuppressive therapy. Immunosuppressive therapy consisted of prednisone with either cyclosporine or azathioprine. The primary outcome measure was a change in the left ventricular ejection fraction at 28 weeks.

*Results.* In the group as a whole, the mean ( $\pm$ SE) left ventricular ejection fraction improved from  $0.25 \pm 0.01$  at base line to  $0.34 \pm 0.02$  at 28 weeks ( $P < 0.001$ ). The mean change in the left ventricular ejection fraction at 28 weeks did not differ significantly between the group of pa-

tients who received immunosuppressive therapy (a gain of 0.10; 95 percent confidence interval, 0.07 to 0.12) and the control group (a gain of 0.07; 95 percent confidence interval, 0.03 to 0.12). A higher left ventricular ejection fraction at base line, less intensive conventional drug therapy at base line, and a shorter duration of disease, but not the treatment assignment, were positive independent predictors of the left ventricular ejection fraction at week 28. There was no significant difference in survival between the two groups ( $P = 0.96$ ). The mortality rate for the entire group was 20 percent at 1 year and 56 percent at 4.3 years. Features suggesting an effective inflammatory response were associated with less severe initial disease.

*Conclusions.* Our results do not support routine treatment of myocarditis with immunosuppressive drugs. Ventricular function improved regardless of whether patients received immunosuppressive therapy, but long-term mortality was high. (*N Engl J Med* 1995;333:269-75.)

MYOCARDITIS is a precursor of dilated cardiomyopathy.<sup>1-3</sup> Aberrant cellular and humoral immune responses have been proposed as possible mechanisms in postviral myocarditis,<sup>4-7</sup> and immunosuppressive therapy has appeared to improve the course of the disease.<sup>8-11</sup> The efficacy of immunosuppression, however, has not been clearly established.

The Myocarditis Treatment Trial<sup>12-14</sup> was designed to evaluate the efficacy of immunosuppression in patients with myocarditis and to identify immunologic markers of the severity of the disease and the response to therapy. In this report we describe the results of the clinical trial and explore the relation between the outcomes

and the clinical, histologic, and immunologic characteristics of the patients.

## METHODS

### Enrollment and Randomization

The design and methods of the trial are fully described elsewhere.<sup>14</sup> Patients with an onset of heart failure during the two years preceding enrollment but without coronary artery disease or another specific cause were enrolled at 31 centers in the United States, Canada, and Japan, as well as through an open-enrollment process.<sup>14</sup> Pathologists at the centers found histopathological evidence of myocarditis on endomyocardial biopsy in 214 of 2233 patients (10 percent). Thirty of the 214 patients had left ventricular ejection fractions greater than or equal to 0.45, as determined by radionuclide gated blood-pool imaging, and 44 met one or more medical criteria for exclusion<sup>14</sup>; an additional 29 patients declined enrollment. The remaining 111 patients with histologic evidence of myocarditis and left ventricular ejection fractions under 0.45 were randomly assigned in equal proportions to one of three treatment groups. One group received azathioprine and prednisone, another group received cyclosporine and prednisone, and the third group did not receive any immunosuppressive therapy. After the first 58 patients had been enrolled, random assignment to the azathioprine-prednisone group was discontinued in order to reduce the number of patients required for the trial.

At the time of the base-line endomyocardial biopsy, right-heart catheterization was performed, and blood samples were obtained for

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\*The centers and investigators participating in the Myocarditis Treatment Trial are listed in the Appendix.

chemical and immunologic studies. Echocardiography and an exercise stress test were performed within two weeks before or after the base-line biopsy.

### Therapy

Treatment in all three groups included a stepped regimen of conventional drugs for heart failure, with each successive drug added to the existing, tolerated regimen. The stepped regimen allowed the calculation of a score for the intensity of the therapy.<sup>14</sup> In the control group patients received only conventional therapy. In the azathioprine-prednisone group, patients received 1 mg of azathioprine per kilogram of body weight twice daily for 24 weeks. Prednisone was started at a dose of 1.25 mg per kilogram per day, in divided doses, and was maintained at that level for one week. The dose was then decreased by approximately 0.08 mg per kilogram per week until the dose was 0.33 mg per kilogram per day at the end of week 12. This reduced dose was maintained through the end of week 20, after which it was reduced by 0.08 mg per kilogram per week until the end of week 24, when the drug was discontinued.

In the cyclosporine-prednisone group, cyclosporine was started at a dose of 5 mg per kilogram given orally twice a day. The dose was adjusted to achieve a concentration of 200 to 300 ng per milliliter at the end of week 1, as determined by radioimmunoassay of whole blood at room temperature. The dose was then tapered to achieve a blood level between 100 and 200 ng per milliliter during weeks 2 through 4. From the end of week 4 to the end of week 24, the blood level was maintained between 60 and 150 ng per milliliter. The initial dose of prednisone in this group was the same as that in the azathioprine-prednisone group. After one week, the dose was rapidly tapered to a level of 0.15 mg per kilogram per day by the end of week 3. This dose was maintained through week 23 and then halved for a week. The drug was discontinued at the end of week 24.

### Endomyocardial Biopsy and Histopathological Studies

The majority of the biopsies were performed with the Stanford technique<sup>15</sup> and the Stanford-Scholten bioptome (Scholten Instruments, Palo Alto, Calif.). At least four specimens were obtained from each patient for light microscopical evaluation with hematoxylin and eosin and Masson trichrome stains.

Pathologists at the participating centers were instructed in the use of the Dallas criteria<sup>16,17</sup> for the diagnosis of myocarditis. The pathologist at each center evaluated the biopsy specimens from candidates for the trial, and eligibility for randomization was determined on the basis of that evaluation. At a later date, the biopsy specimens were reviewed by a panel of seven pathologists experienced in the interpretation of histologic features of endomyocardial-biopsy specimens and in the application of the Dallas criteria.<sup>16,17</sup> The final diagnosis was based on the consensus of the panel. Initial biopsy specimens were categorized as showing myocarditis, borderline myocarditis, or no myocarditis. When myocarditis was present, it was characterized as diffuse or focal. Subsequent biopsy specimens were categorized as showing ongoing, healing, healed, or recurrent myocarditis.

### Immunologic Studies

Serum obtained at base line and follow-up was submitted to two laboratories for the measurement of antibodies to cardiac and non-cardiac antigens by indirect immunofluorescence, as described elsewhere.<sup>14,18,19</sup> The technique we used to measure anti-cardiac IgG antibodies may not exclude anti-skeletal-muscle IgG antibodies in some cases. We use the term "general IgG antibodies" to refer to antibodies to skeletal and smooth muscle, nuclei, mitochondria, and parietal cells. Blood samples were submitted to a third laboratory for the measurement of cellular immune markers by a variety of techniques, including flow cytometry and assays of antibody-dependent cellular cytotoxicity and natural-killer-cell activity.<sup>14</sup>

### Follow-up

At weeks 12, 28, and 52, the left ventricular ejection fraction was determined by radionuclide ventriculography. Echocardiography, exercise testing, endomyocardial biopsies, and blood studies were also performed. Between weeks 24 and 52, immunosuppressive therapy

was withheld while the regimen of conventional therapy was followed. After 52 weeks, each patient's vital status was monitored regularly until the end of the trial, but rigid control of conventional therapy was suspended.

### Statistical Analysis

Our primary objective was to compare the effects of immunosuppressive therapy combined with conventional therapy and conventional therapy alone on the left ventricular ejection fraction between the time of enrollment and week 28, according to an intention-to-treat strategy. We estimated the sample size required for a two-tailed significance level of 0.05 and a power of 0.80. The two immunosuppression groups were combined for all analyses, since there were no differences in their clinical characteristics or outcomes after random assignment of the first 58 patients or after random assignment of all 111 patients, and there was no evidence that the two immunosuppressive regimens had different effects in subgroups of patients.

The primary analysis was an analysis of covariance with a linear model, which assessed the effect of treatment after adjustment for the left ventricular ejection fraction and other characteristics at base line. For the 10 patients who died, the 4 patients who underwent cardiac transplantation, and the 1 patient in whom treatment failed<sup>14</sup> before the evaluation of left ventricular ejection fraction at 28 weeks, the most recently determined values for the ejection fraction were used in the analysis. A similar analysis was performed for the change in the ejection fraction at week 52. The effects of treatment on secondary measures of ventricular function (echocardiographic determination of the left ventricular internal diameter at end diastole and pulmonary-capillary wedge pressure) were analyzed in a similar way.

A second objective of the trial was to examine immune-activation measures as possible markers of the severity of disease and as predictors of the response to therapy. Each of five indexes of disease severity (left ventricular ejection fraction, left ventricular internal diameter at end diastole, pulmonary-capillary wedge pressure, conventional-therapy score, and duration of symptoms at the time of enrollment) was assessed as the dependent variable in a separate linear or logistic-regression model, with backward elimination, that initially included only the immunologic markers. We report the results of these analyses both before and after other correlates of the severity of disease (pulmonary-artery mean pressure, cardiac index, heart rate, and New York Heart Association class) were added to the models as independent variables.

Other secondary objectives of the trial were to compare survival in the treatment groups and to evaluate changes over time in endomyocardial-biopsy specimens, the intensity of conventional therapy, and immunologic markers. All patients were included in the survival analyses, and those who died or underwent cardiac transplantation were considered to have reached a mortality end point. Survival at one year was evaluated by censoring data for all patients who survived for a longer period. Cox proportional-hazards regression models were used to compare survival in the groups after adjustment for the effects of other patient characteristics. Survival probabilities were estimated with the Kaplan-Meier method. Means and proportions were compared with standard statistical tests for continuous and categorical data. SAS software<sup>20</sup> was used for all analyses.

## RESULTS

### Clinical Characteristics

There were no significant differences in clinical characteristics between the treatment groups (Table 1). The mean ( $\pm$ SD) left ventricular ejection fraction for the overall group of patients was  $0.24 \pm 0.10$ , and most of the patients were in New York Heart Association class II or III.

### Changes in Left Ventricular Function

We analyzed changes after therapy in three indexes of left ventricular function: left ventricular ejection

**Table 1. Initial Demographic, Clinical, Histopathological, and Immunologic Characteristics of 111 Patients with Myocarditis.\***

CHARACTERISTIC	IMMUNOSUPPRESSION GROUP (N = 64)		CONTROL GROUP (N = 47)	
	NO. OF PATIENTS	VALUE	NO. OF PATIENTS	VALUE
<b>Demographic</b>				
Age — yr	64	43±14	47	41±13
Female sex — %	64	42.2	47	31.9
<b>Clinical</b>				
Left ventricular ejection fraction	63	0.24±0.11	47	0.24±0.09
NYHA class — %	62		45	
I		14.5		15.6
II		38.7		28.9
III		38.7		42.2
IV		8.1		13.3
Right atrial pressure — mm Hg	59	8±6	42	9±7
Pulmonary-capillary wedge pressure — mm Hg	60	20±9	44	18±9
Cardiac index — liters/min/m <sup>2</sup>	55	2.3±0.8	42	2.5±0.8
Left ventricular internal diameter — mm	49	64±10	35	64±9
Exercise time — min	54	9±5	36	10±6
Conventional-therapy score†	63	6±3	46	6±3
Duration of presenting symptoms ≤1 mo — %	63	42.9	47	51.1
History of viral illness — %	60	86.7	43	93.0
<b>Histopathological (Dallas criteria) — %‡</b>				
Criteria met	61	60.7	46	67.4
Criteria met with diffuse lymphocytic infiltrate	30	23.3	27	18.5
<b>Immunologic</b>				
Elevated erythrocyte sedimentation rate — %	50	54.6	33	52.0
White-cell count — ×10 <sup>-3</sup> /mm <sup>3</sup>	58	8±3	43	9±3
Fever — %	53	20.8	36	16.7
Cardiac IgG antibody titer ≥1:10 — %	51	52.9	35	74.3
Skeletal-muscle IgG antibody titer >1:10 — %	51	15.7	35	37.1§
General IgG antibody titer ≥1:40 — %	45	31.1	30	40.0
Natural killer cells — lytic units, %¶	40	2.3±1.0	33	2.3±0.9
Helper T cells (Leu-3a+) ≥0.30 — %	41	48.8	33	51.5
CD2+ T cells (Leu-5b+) — no./mm <sup>3</sup> ¶	40	6.8±0.9	32	6.9±0.9
Natural killer cells and macrophages (Leu-11b+) — no./mm <sup>3</sup> ¶	37	3.9±1.2	32	4.1±1.5

\*Plus-minus values are means ±SD. For each variable, the numbers of patients for whom data were available are indicated. NYHA denotes New York Heart Association.

†A score of 6 includes reduced salt intake and use of digoxin, furosemide (100 to 160 mg per day), and an angiotensin-converting-enzyme inhibitor.

‡The Dallas criteria include the presence of a lymphocytic infiltrate and associated myocyte necrosis.<sup>16,17</sup>

§P=0.039.

¶Log-transformed values.

fraction, left ventricular internal diameter at end diastole, and pulmonary-capillary wedge pressure. There was no difference between the two groups in the mean left ventricular ejection fraction at base line, week 28, or week 52 (Fig. 1). The primary analysis of changes in left ventricular ejection fraction after therapy (with data from 89 patients at week 28 and with data from 84 patients at week 52) also showed no significant differences (Fig. 1). The left ventricular ejection fraction improved in both treatment groups during the course of the trial. The mean (±SE) base-line left ventricular ejection fraction was 0.24±0.01 in the immunosuppression group (54 patients), with a mean increase at 28 weeks of 0.10 (95 percent confidence interval, 0.07 to 0.12), and it was 0.26±0.01 in the control group (35 patients), with a mean increase of 0.07 (95 percent confidence interval, 0.03 to 0.12). The increase in the mean left ventricular ejection fraction achieved by week 28 was maintained in the group as a whole and

actually increased further (P=0.03) through week 52.

A multivariate covariance analysis showed that therapy had no significant effect on the change in the left ventricular ejection fraction at week 28 (P=0.30). As expected, the initial value for the left ventricular ejection fraction was strongly associated with the subsequent value. After adjustment for base-line left ventricular function, several variables predicted the left ventricular ejection fraction at week 28. Patients receiving less intensive conventional therapy at the time of enrollment had higher left ventricular ejection fractions at week 28 than those receiving more intensive conventional therapy (P=0.04). Patients with disease of one month's duration or less at the time of enrollment also had a greater improvement in the left ventricular ejection fraction than those with a longer duration of disease (P=0.007). A similar multivariate analysis showed that therapy had no significant independent effect on the left ventricular ejection fraction at week 52.

Like the left ventricular ejection fraction, the pulmonary-capillary wedge pressure was improved at week 28, and the extent of the change did not differ significantly between the two groups (P=0.25). The mean (±SD) left ventricular internal diameter at end diastole was higher in the immunosuppression group than in the control group at week 28 (64±2 mm vs. 59±2 mm, P=0.05).

We investigated the possibility that more intensive conventional therapy for heart failure during the course of the trial accounted for the observed improvement in the left ventricular ejection fraction. However, we found that a decrease in the intensity of conventional therapy at week 28, in comparison with the base-line intensity, was correlated with a higher left ventricular ejection fraction, and an increase in the intensity of conventional therapy was correlated with a lower left ventricular ejection fraction.

### Survival

Figure 2 compares actuarial survival in the two groups. There were 34 deaths and 10 cardiac transplantations among the 111 patients. The immunosuppression and control groups did not differ significantly in survival at one year (P=0.62) or throughout the period of follow-up (P=0.96) (Table 2). The base-line left ventricular ejection fraction was positively associated

with the duration of survival ( $P < 0.001$ ), and the intensity of conventional therapy at base line was negatively associated with survival ( $P = 0.003$ ).

**Adverse Drug Effects**

An increase in the creatinine level by at least 0.5 mg per deciliter during therapy was more common in the cyclosporine-prednisone group (46 percent of the patients) than in the control group (9 percent) or the azathioprine-prednisone group (16 percent) ( $P < 0.001$ ), but no patients were withdrawn because of renal dysfunction. The incidence of new hypertension (14 percent) or severe infection (6 percent) did not differ significantly among the three groups.

**Endomyocardial-Biopsy Findings**

Base-line histopathological findings in endomyocardial-biopsy specimens are summarized in Table 1. At the time of enrollment, all 111 patients were considered to have histopathological evidence of myocarditis. Sixty-

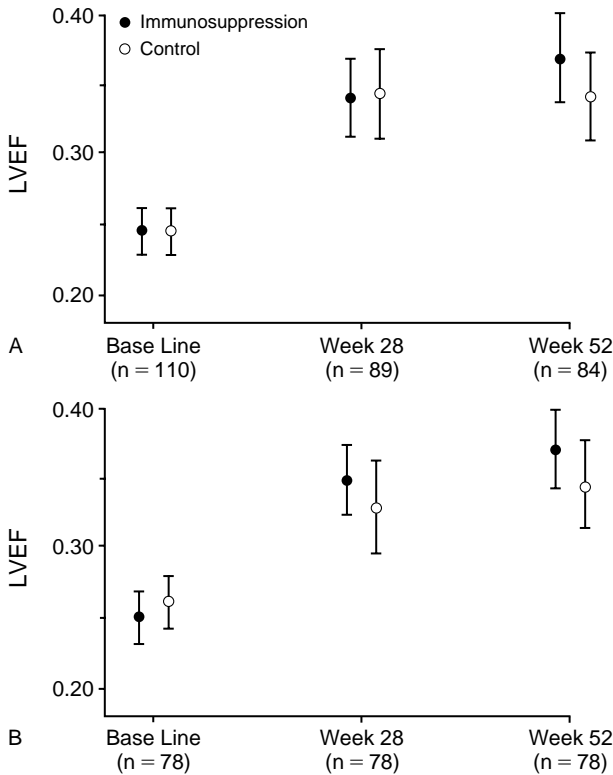
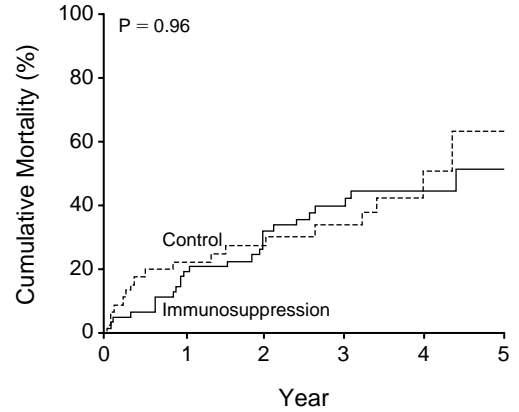


Figure 1. Mean (±SE) Left Ventricular Ejection Fraction (LVEF) in the Immunosuppression and Control Groups at Base Line, Week 28, and Week 52.

Panel A shows the mean values for all available studies at each time, with the numbers of patients indicated at the bottom of the panel. There was no difference between the two groups in the mean LVEF at base line, week 28, or week 52 ( $P = 0.97$ ,  $P = 0.95$ , and  $P = 0.45$ , respectively). Panel B shows the mean values for the 78 patients in whom data were available at all three times. Again, there was no significant difference between the groups ( $P = 0.51$ ,  $P = 0.60$ , and  $P = 0.50$ , respectively).



Immuno-suppression	64	49	37	23	12	0
Control	47	32	23	16	6	0

Figure 2. Actuarial Mortality (Defined as Deaths and Cardiac Transplantations) in the Immunosuppression and Control Groups.

The numbers of patients at risk are shown at the bottom. There was no significant difference in mortality between the two groups.

four percent of the biopsy specimens from the 107 patients in whom adequate slides were available for review were later judged by the Pathology Panel to meet the Dallas criteria<sup>16</sup> for myocarditis or borderline myocarditis. In most cases, disagreement with the diagnosis of myocarditis by a pathologist at a participating center resulted from the panel's judgment that myocyte necrosis was not clearly present. Sixty biopsy specimens obtained at week 28 were available for review by the Pathology Panel. Only two specimens showed ongoing evidence of myocarditis, and in one of the two the diagnosis was borderline myocarditis. At week 52, 45 biopsy specimens were available. Four specimens showed evidence of myocarditis: borderline in one, ongoing in one, and recurrent in two.

**Immune Activation, Disease Severity, and Outcome**

Selected indexes of immune activation are listed in Table 1. The treatment groups were similar with respect to most of these indicators. Associations between these indexes and objective measures of the severity of disease are shown in Table 3. Several associations suggest that disease at the time of enrollment in the trial was less severe in patients who had a more robust inflammatory response. A higher level of cardiac IgG antibodies was associated with a higher left ventricular ejection fraction and a smaller left ventricular size. A higher level of general IgG antibodies was associated with a lower pulmonary-capillary wedge pressure. A higher level of anti-skeletal-muscle IgG antibodies was associated with a shorter duration of disease. A higher white-cell count was correlated with a smaller left ventricular internal diameter at end diastole. A higher level of natural killer cells and macrophages (Leu-11b+

**Table 2. Multivariate Cox Model for Mortality among 109 Patients with Myocarditis.\***

VARIABLES IN MODEL	RISK RATIO (95% CI)	P VALUE
<b>Initial variables</b>		
Immunosuppression group (vs. control group)	0.98 (0.52–1.87)	0.96
Base-line left ventricular ejection fraction†	0.90 (0.87–0.94)	<0.001
Conventional-therapy score at base line‡	1.17 (1.06–1.31)	0.003
<b>Additional variables§</b>		
CD2+ (Leu-5b+) T-cell count	2.25 (1.18–4.31)	0.01

\*The model was stratified according to enrollment center. CI denotes confidence interval.

†The risk ratio is for each increase of 0.01 in the left ventricular ejection fraction.

‡The risk ratio is for each increase of 1 in the conventional-therapy score.

§The addition of the CD2+ T-cell count to the model reduced the number of patients in the analysis to 72. The estimates for the first three variables did not change substantially. The risk ratio is for each increase of 1 in the log-transformed value for the number of cells per cubic millimeter.

cells) was associated with a longer exercise time and less intensive conventional drug therapy for heart failure. However, a lower level of helper T cells (Leu-3a+ cells) was also associated with less intensive conventional therapy. Six of the eight associations were still significant after adjusting for clinical characteristics. There was no systematic change in the immunologic variables during follow-up.

The effects of these immunologic variables on outcome were also evaluated. After adjustment for the treatment-group assignment and the base-line values for the continuous outcome measures, the immunologic variables were added to the separate multivariate models previously developed for each measure of cardiac performance (left ventricular ejection fraction, left ventricular internal diameter at end diastole, and pulmonary-capillary wedge pressure) and survival. None of the variables were significantly associated with the measures of cardiac performance in the group of patients as a whole. A higher peripheral-blood CD2+ T-lymphocyte count (Leu-5b+ cells) was associated with a higher risk of death (Table 2).

## DISCUSSION

Immunosuppression did not have a beneficial effect on the primary end point, a change in the left ventricular ejection fraction at 28 weeks, and actually had a statistically significant, though clinically mild, negative influence on the left ventricular internal diameter at end diastole. Immunosuppression also did not improve survival. We conclude that immunosuppressive therapy is not beneficial in most patients with histologically confirmed myocarditis.

We cannot be dogmatic, however, in advising the withholding of immu-

nosuppressive therapy in all patients with myocarditis, for several reasons. Numerous viruses can cause myocarditis, and they vary in their prevalence, virulence, and responsiveness to immunosuppressive therapy, both geographically and temporally. Our definition of myocarditis included a left ventricular ejection fraction that was less than 0.45, a duration of illness of less than two years, and an endomyocardial biopsy that was indicative of myocarditis, according to an experienced pathologist. There may be other ways to identify myocarditis. Of course, our findings do not apply to patients with other forms of histologically confirmed myocarditis that we did not study, including giant-cell myocarditis, peripartum myocarditis, hypersensitivity myocarditis, and cardiac sarcoidosis. Thus, the patients we studied may not be representative of all patients with myocarditis. Finally, the immunosuppressive therapies that we used — the drugs, dosages, and duration of their administration — cannot be considered representative of all immunosuppressive strategies.

As we have noted elsewhere,<sup>14,21</sup> there was a low incidence of histologic evidence of myocarditis (10 percent) in the 2233 patients undergoing biopsy specifically to rule out this diagnosis. Thus, the assumption should never be made that a patient presenting with clinical findings consistent with myocarditis has microscopical evidence of the disease. Although an endomyocardial biopsy is required for histologic confirmation of the diagnosis, the need for a routine biopsy when myocarditis is suspected is mitigated by the facts that histologic evidence of myocarditis is found infrequently and there is

**Table 3. Multivariate Analysis of Associations between the Severity of Initial Disease and Markers of Immune Activation.\***

SEVERITY OF INITIAL DISEASE	NO. OF PATIENTS	MARKERS OF IMMUNE ACTIVATION PREDICTING LESS SEVERE DISEASE	PARAMETER ESTIMATE (95% CI)	P VALUE	R <sup>2</sup>
Higher left ventricular ejection fraction	60	Cardiac IgG antibody titer ≥1:10†	9.28 (4.50 to 14.05)	<0.001	0.20
Smaller left ventricular internal diameter	38	Cardiac IgG antibody titer ≥1:10	-7.28 (-12.29 to -2.27)	0.007	
		Higher white-cell count†	-1.86 (-2.70 to -1.03)	<0.001	0.43
Lower pulmonary-capillary wedge pressure	52	General IgG antibody titer ≥1:40	-7.48 (-12.80 to -2.15)	0.008	0.13
Longer exercise time	57	Higher level of natural killer cells†	1.33 (0.07 to 2.59)	0.04	0.07
Less intensive conventional therapy	51	Higher levels of natural killer cells and macrophages†	-0.92 (-1.54 to -0.30)	0.006	
		Helper T-cell count <30%†	-1.95 (-3.60 to -0.29)	0.03	0.19
Duration of symptoms ≤1 mo	50	Skeletal-muscle IgG antibody titer >1:10†	5.27 (1.38 to 20.10)‡	0.02	NA §

\*The data were derived from analyses in which each indicator of the severity of initial disease was assessed as the dependent variable in a separate linear- or logistic-regression model, with backward elimination that included only immunologic markers. The parameter estimates indicate the effects of the immunologic markers on the severity of initial disease. R<sup>2</sup> denotes the correlation coefficient.

†The association remained significant (P<0.05) after the addition of other clinical variables, including those known to be correlated with the severity of left ventricular dysfunction.

‡Odds ratio.

§Logistic-regression model.

no therapy for the condition. The patients who had negative biopsy results in our study may have had idiopathic dilated cardiomyopathy or a form of myocarditis that was not detected by endomyocardial biopsy. Our findings are not applicable to patients thought to have myocarditis without histologic evidence of it.

A multivariate analysis identified a better base-line left ventricular ejection fraction, less intensive conventional therapy at base line, and a shorter duration of disease as independent predictors of improvement in the left ventricular ejection fraction. These results and the multivariate predictors of mortality that we identified (Table 2) were not surprising. The left ventricular ejection fraction is a well-known predictor of survival, and more intensive therapy for heart failure would be expected in patients with more severe disease and a poorer prognosis.

Features consistent with a stronger immune response were associated with less severe initial disease. Table 3 shows the results of multivariate analyses of the association of immunologic variables with six measures of the initial severity of disease. Increased natural-killer-cell activity and a higher white-cell count are consistent with a more effective inflammatory response. Though we did not measure antiviral antibodies specifically, the increased IgG antibody levels that we observed may also be indicative of an inflammatory response. These observations suggest that in patients with myocarditis, a prominent immunologic response may be a benefit rather than a principal cause of the disease. Although the presence of cardiotropic virus and a virus-specific immune response was not assessed in this study, enteroviruses are thought to be associated with most cases of myocarditis in humans. In the earliest phase of viral myocarditis, the virus replicates in cardiac tissue and elicits a cellular response (predominantly natural killer cells and macrophages) and a humoral immune response.<sup>3</sup> If this response is adequate, the virus is largely or completely eliminated from the heart, and recovery is possible. If the initial immune response is insufficient, however, the virus is not eliminated, and either direct myocardial damage continues<sup>22</sup> or an autoimmune process may develop. In the latter case, a chronic, destructive immune reaction, mediated primarily by T lymphocytes and characterized by various manifestations of autoimmunity and myocytolytic activity, may ensue and cause further myocyte injury.<sup>4,23,24</sup> Allosensitized T lymphocytes have recently been shown to cause both reversible and irreversible myocyte dysfunction through direct contact between cells.<sup>25</sup> These findings are consistent with our observation that higher levels of helper T cells were associated with more severe initial disease, as indicated by the need for more intensive conventional therapy of heart failure, and that higher levels of circulating CD2+ T cells were associated with a greater risk of death.

Thus, our data support the interpretation that an early, appropriate inflammatory response has a bene-

ficial effect in patients with myocarditis. In some patients, however, heightened T-cell activity may be deleterious. This interpretation does not preclude the possibility that appropriately timed immunosuppressive treatment would be helpful in some patients with myocarditis, if it prevented or ameliorated the harmful T-cell response.<sup>23,25</sup>

Although the results of this trial do not suggest new options for treatment, they do suggest that a distinct subgroup of patients with myocarditis, identified on the basis of serologic and cellular indicators of heightened immune activity, has less severe disease. However, the rate of mortality (which we defined as death or the need for cardiac transplantation) reached 56 percent at four years. Myocarditis is often a devastating illness that evolves into a chronic, progressive disease with a prognosis similar to that of idiopathic dilated cardiomyopathy.<sup>26</sup> Thus, although some patients have an appropriate, early immune response, many have a response that is inadequate to prevent permanent cardiac injury.

#### APPENDIX

The centers and investigators participating in the Myocarditis Treatment Trial are listed below, with the number of patients randomized at each center given in parentheses (15 further patients were received in open enrollment). For each center, the first person listed was the principal investigator. *Loyola University Medical Center, Maywood, Ill.* (12): M.R. Costanzo and K. Grady; *Winthrop University Hospital, Mineola, N.Y.* (10): N.E. Kantrowitz, S.M. Zeldis, S. Kane, M.E. Coglianesi, C. Tomeo, and K. Bacon; *Toronto Hospital, Toronto* (8): P.R. McLaughlin, P. Liu, and B. Ross; *Massachusetts General Hospital, Boston* (7): I.F. Palacios, W. Dec, B. Block, and D. Cocca-Spoffard; *Baylor College of Medicine, Houston* (6): J.B. Young, C. Leon, R. Casta, and C. Kingry; *St. Luke's Episcopal Hospital, Houston* (6): N.E. Strickman and M. Harlan; *University of Cincinnati, Cincinnati* (5): N. Fowler, P. Engel, and N. Nunn; *University of Michigan, Ann Arbor* (5): S.K. Das, P. Suh, E. Kline, and A.J. Gilles; *Harbor-UCLA Medical Center, Torrance* (4): W. J. French and A. Skinner; *Ohio State University College of Medicine, Columbus* (4): D.V. Unverferth, R. Starling, P. Newton, and M. Wooding-Scott; *Pennsylvania Hospital, Philadelphia* (4): W.J. Untereker, D. Poll, K. Hoffman, and J. Frank; *University of Utah, Salt Lake City* (4): J.W. Mason, J.B. O'Connell, R. Fowles, K. Millar, L. Freedman, and S. Lyver; *Brooke Army Medical Center, Fort Sam Houston, Tex.* (3): R. Latham and R. Peeples; *Minneapolis Heart Institute Foundation, Minneapolis* (3): I.F. Goldenberg, D. Hunn, and P. Anderson; *New York Medical College, Valhalla* (3): M.B. Weiss and N. Truelieb; *Oregon Health Sciences University, Portland* (3): J. Hosenpud, R. Conner, and L.J. Brown; *University of Tennessee, Memphis* (2): K.B. Ramanathan, C. Pounders, M. Mills, and K. Kantor; *Beth Israel Hospital, Boston* (1): W.H. Abelmann, A. Flaherty, and K. Thorp; *Beth Israel Medical Center, New York* (1): J. Strain, P. Virzi, A. Grayeski, and A. Kelly; *Cleveland Clinic Foundation, Cleveland* (1): R.E. Hobbs and D. Pelegrin; *Mount Sinai Medical Center, New York* (1): M. Cohen and L. Hawkins; *University Hospital, London, Ont., Canada* (1): W.J. Kostuk and R. Kennedy; *University of Connecticut, Farmington* (1): W.D. Hager, J. Dougherty, A. Riba, S. Larkin, and L. Kearney; *University of Ottawa Heart Institute, Ottawa, Ont.* (1): R.A. Davies and K. Drouin; *Kyoto University, Kyoto, Japan* (0): A. Matsumori; *Montefiore Hospital, New York* (0): R.M. Grose and B. Levine; *Presbyterian University Hospital, Pittsburgh* (0): B.F. Uretsky, S. Murali, and A. Betschart; *St. Louis University Medical Center, St. Louis* (0): G.A. Williams, L. Miller, and S. Wittry; *Tulsa Heart Institute, Tulsa, Okla.* (0): A.D. Hagan and J. Durham; *University of California, San Diego* (0): R. Shabetai and R. Cremo, and *University of Nebraska Medical Center, Omaha* (0): B.M. McManus, T. Sears, and W. Arteaga.

*Clinical Coordinating Center (University of Utah):* J.W. Mason and J.B.

O'Connell; *Data Coordinating Center (University of Arizona)*: T. Moon, E. Hahn, V. Hartz, A. Rico, and N. Jenrow; *Core Immunology Laboratory (Johns Hopkins University)*: N.R. Rose, A. Herskowitz, C.L. Burek, P. Jones, and M. Vladut-Talor; *Core Immunology Laboratory (University of Nebraska Medical Center)*: B.M. McManus, J. Wilson-McManus, B. Switzer, and K. Guy; *Pathology Panel*: M.E. Billingham (chair), H.T. Aretz, W.B. Edwards, S. Factor, J. Fallon, M.E. Hammond, B.M. McManus, and F. Schoen; *Safety Monitoring Committee*: G.S. Francis (chair), H. Burchell, B.H. Brundage, S. Goldstein, R. Luepker, and P. Miller.

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