

Controlled Trial of Intravenous Immune Globulin in Recent-Onset Dilated Cardiomyopathy

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Background—This prospective placebo-controlled trial was designed to determine whether intravenous immune globulin (IVIG) improves left ventricular ejection fraction (LVEF) in adults with recent onset of idiopathic dilated cardiomyopathy or myocarditis.

Methods and Results—Sixty-two patients (37 men, 25 women; mean age \pm SD 43.0 \pm 12.3 years) with recent onset (\leq 6 months of symptoms) of dilated cardiomyopathy and LVEF \leq 0.40 were randomized to 2 g/kg IVIG or placebo. All underwent an endomyocardial biopsy before randomization, which revealed cellular inflammation in 16%. The primary outcome was change in LVEF at 6 and 12 months after randomization. Overall, LVEF improved from 0.25 \pm 0.08 to 0.41 \pm 0.17 at 6 months (P <0.001) and 0.42 \pm 0.14 (P <0.001 versus baseline) at 12 months. The increase was virtually identical in patients receiving IVIG and those given placebo (6 months: IVIG 0.14 \pm 0.12, placebo 0.14 \pm 0.14; 12 months: IVIG 0.16 \pm 0.12, placebo 0.15 \pm 0.16). Overall, 31 (56%) of 55 patients at 1 year had an increase in LVEF \geq 0.10 from study entry, and 20 (36%) of 56 normalized their ejection fraction (\geq 0.50). The transplant-free survival rate was 92% at 1 year and 88% at 2 years.

Conclusions—These results suggest that for patients with recent-onset dilated cardiomyopathy, IVIG does not augment the improvement in LVEF. However, in this overall cohort, LVEF improved significantly during follow-up, and the short-term prognosis remains favorable. (*Circulation*. 2001;103:2254-2259.)

Key Words: cardiomyopathy ■ immune system ■ myocarditis ■ biopsy

Idiopathic dilated cardiomyopathy is a serious disorder and the most common cause of heart failure in young patients requiring cardiac transplantation.¹ Although up to 25% of dilated cardiomyopathies may be genetic in origin,² the majority are sporadic, and a viral or immune pathogenesis is suspected. Despite this, cellular inflammation is confirmed by biopsy in only a minority of patients, and immunosuppressive therapy has not proved efficacious in previous randomized trials.^{3,4}

High-dose intravenous immune globulin (IVIG) has both antiviral and immune modulatory effects and is an important therapy for Kawasaki disease,⁵ a coronary vasculitis of children. Its utility for this disorder led to its use in children with new-onset dilated cardiomyopathy and myocarditis. Drucker et al⁶ reported a series of children treated with immune globulin in whom significant improvements in left ventricular function were seen compared with recent historical controls. We subsequently reported 2 uncontrolled series

of adults with recent-onset dilated cardiomyopathy⁷ and peripartum cardiomyopathy⁸ who were treated with immune globulin and had substantial recovery of left ventricular function during follow-up.

A prospective, randomized study was performed to evaluate the potential role of this therapy. The Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) trial was initiated in 1996 to examine the impact of immune globulin on recovery of left ventricular function in adult patients with recent-onset dilated cardiomyopathy.

Methods

Study Design

The study design was a prospective, randomized, placebo-controlled, double-blind evaluation of the addition of IVIG to conventional therapy in adult patients with new-onset dilated cardiomyopathy. The primary inclusion criteria were a left ventricular ejection fraction

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(LVEF) ≤ 0.40 , an evaluation consistent with either idiopathic dilated cardiomyopathy or myocarditis, and no more than 6 months of cardiac symptoms at the time of randomization. All patients underwent angiography or noninvasive screening to exclude coronary artery disease, a transthoracic echocardiogram to rule out significant valvular disease, and a right ventricular endomyocardial biopsy before enrollment. Patients with significant diabetes (requiring therapy with insulin or an oral agent for more than 1 year), significant hypertension (diastolic pressure >95 mm Hg or systolic pressure >160 mm Hg) or uncorrected thyroid disease were excluded. Patients with and without cellular inflammation on biopsy were eligible for inclusion; however, patients with giant cell myocarditis, sarcoid, or hemochromatosis were excluded.

Treatment-group assignment was performed with a blocked randomization scheme (initial block of 2 treatment assignments followed by blocks of 4) stratified by clinical center. Patients randomized to the treatment group received a total of 2 g/kg IVIG (Gamimune N, 10%, Bayer Corporation). This was administered at 1 g/kg IV each day on 2 consecutive days. Patients randomized to placebo received 0.1% albumin in 10% maltose solution given in an equivalent volume (10 mL/kg IV each day on 2 consecutive days).

Functional Assessment and Follow-Up

LVEF was assessed at baseline by radionuclide angiography, which was repeated at 6 and 12 months after randomization. Left ventricular dimensions were assessed by transthoracic echocardiogram before randomization. Patients not on mechanical support had an assessment of functional capacity by metabolic stress testing at baseline, as well as a 6-minute walk test. Metabolic stress testing was repeated 12 months after randomization, and the 6-minute walk was repeated at 1, 6, and 12 months.

Patients were seen during follow-up at 1, 6, and 12 months after randomization at the enrolling IMAC center. Patients were followed up at 6-month intervals after the first year, and the occurrence of the secondary end point of death, cardiac transplantation, or need for left ventricular assist device (LVAD) was noted. Follow-up for secondary end-point status was 100% complete as of June 1999.

Statistical Analysis

The primary end point was predetermined as the change in LVEF from baseline to 6 and 12 months after randomization. Secondary end points were event-free survival (events defined as death, cardiac transplantation, or placement of an LVAD) and comparison of functional capacity as assessed by metabolic stress testing at 12

TABLE 1. IMAC Study Population Baseline Evaluation

	IVIG (n=33)	Placebo (n=29)	All Patients (n=62)
Demographics/symptoms			
Age, y	42.1±12.1	44.0±12.6	43.0±12.3
Female, n (%)	14 (42.4)	11 (37.9)	25 (40.3)
Nonwhite, %	12.1	10.3	11.3
NYHA class, % I/II/III/IV	3/42/48/6	17/48/21/14	10/45/35/10
Duration of symptoms, mo	1.8±1.4	2.2±1.5	2.0±1.5
Flulike illness before symptoms, %	63.6	62.1	62.9
Right heart catheterization and right ventricular biopsy			
PCWP, mm Hg (n=61)	16.3±10.0	15.6±10.2	16.0±10.0
RA, mm Hg (n=61)	8.0±6.8	6.3±5.1	7.2±6.1
CI, L · min ⁻¹ · m ⁻² (n=59)	2.47±0.65	2.43±0.63	2.45±0.64
Abnormal biopsy, %	75.8	86.2	80.6
Fibrosis, %	57.6	69.0	62.9
Hypertrophy, %	42.4	58.6	50.0
Cellular inflammation, %			
Absent	84.8	82.8	83.9
Nonspecific inflammation	3.0	6.9	4.8
Borderline myocarditis	6.1	3.4	4.8
Myocarditis	6.1	6.9	6.5
Radionuclide angiography			
LVEF (n=61)	0.25±0.08	0.25±0.09	0.25±0.08
RVEF (n=48)	0.32±0.11	0.36±0.12	0.34±0.11
Echocardiogram/peak $\dot{V}O_2$			
LV diastolic diameter, cm (n=60)	6.63±0.99	6.65±0.84	6.64±0.92
Peak $\dot{V}O_2$, mL · min ⁻¹ · kg ⁻¹ (n=56)	19.2±6.2	19.7±5.5	19.5±5.8
% Predicted peak $\dot{V}O_2$ (n=56)	72.2±17.5	73.1±30.4	72.7±24.4

RA indicates right atrial pressure; CI, cardiac index; RVEF, right ventricular ejection fraction; peak $\dot{V}O_2$, peak oxygen consumption; and LV, left ventricle.

Continuous data are expressed as mean±SD.

No statistically significant differences were found between the treatment groups with respect to these characteristics.

months after randomization. The study's planned sample size of 30 patients in each treatment arm was calculated to provide 80% power to detect a treatment difference in ejection fraction (EF) change scores of $\geq 8\%$ assuming a within-treatment standard deviation of 10%, using a 2-sided test with significance level of 0.05. These projected differences and variability estimates were based on results reported from the myocarditis treatment trial,⁴ as well as 2 previous retrospective studies of recent-onset dilated cardiomyopathy.^{9,10}

For association of treatment with discrete factors, the χ^2 test was used for dichotomous factors and the Mantel-Haenszel test for ordered categorical factors. For continuous parameters, the overall significance of change from baseline to a follow-up time point was assessed with the Wilcoxon signed rank test, and change scores were compared between treatment groups with the Wilcoxon rank-sum test. Significance of change in 6-minute walk distance over the entire course of follow-up was assessed nonparametrically with the Page test.¹¹ Associations between continuous parameters were assessed via Spearman correlation coefficient. Association of continuous measures with ordered categorical variables such as New York Heart Association (NYHA) class was assessed with the Jonckheere-Terpstra test.¹² Event rates over time were assessed by the Kaplan-Meier method, and the resulting freedom-from-event curves were compared via the log-rank test.

LVEF by radionuclide scan was not available at baseline for 1 patient who was randomized to placebo whose LVEF was 0.30 by left ventricular angiography. This patient has been excluded from analyses involving baseline EF data including the primary end point; deletion of this patient from these analyses did not affect the study findings. This patient has been included in all analyses not involving baseline EF.

Results

Sixty-two adult patients (mean age 43.0 ± 12.3 years) were enrolled at 6 centers between February 1996 and May 1998. The demographics and clinical characteristics of the patients are listed by treatment group in Table 1. Mean LVEF at study entry was 0.25 ± 0.08 , and mean left ventricular end-diastolic diameter was 6.6 ± 0.9 cm. Mean duration of symptoms at the time of randomization was 2.0 ± 1.5 months. Ten (16%) of 62 patients had cellular inflammation on endomyocardial biopsy, including 4 patients with myocarditis and 3 with borderline myocarditis by the Dallas criteria,¹³ as well as 3 with nonspecific inflammation (eg, perivascular lymphocytic infiltration). Although the majority of patients (81%) were NYHA class II or III, 15 (10 IVIG, 5 placebo) required inotropic support and 2 (1 IVIG, 1 placebo) required intra-aortic balloon pump support at the time of initiation of study drug. In contrast, 6 patients (1 IVIG, 5 placebo) were NYHA class I at the time of randomization. There were no significant differences between treatment groups with respect to any of the clinical parameters measured. Conventional therapy at the time of randomization included ACE inhibitors in 56 patients (90%) and β -blocker in 11 patients (18%). There were no adverse events attributed to study drug in either treatment group. Eleven of 33 patients who received IVIG reported minor side effects, predominantly transient flulike symptoms or headache, which were reported in none of the 29 patients who received placebo.

Effect of Therapy on Left Ventricular Function

Mean LVEF for all patients improved significantly from 0.25 ± 0.08 at baseline to 0.41 ± 0.17 at 6 months ($P < 0.001$) and 0.42 ± 0.14 at 12 months after randomization ($P < 0.001$ compared with baseline, $P = \text{NS}$ compared with 6 months).

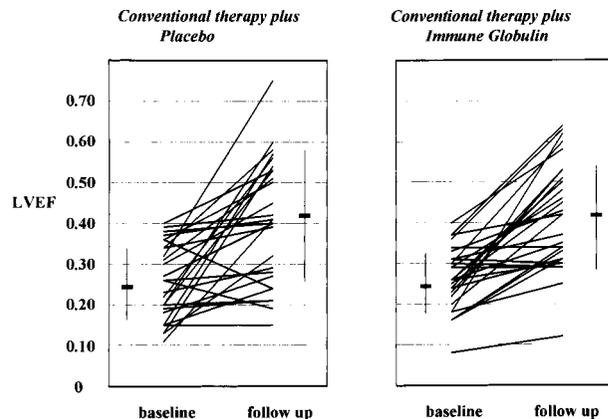


Figure 1. LVEF over time by treatment: LVEF by radionuclide scan at baseline and 12 months after randomization in patients randomized to placebo and IVIG. Overall, LVEF improved significantly over time (12-month LVEF significantly higher than baseline, $P < 0.001$). However, no differences by treatment group were evident ($P = \text{NS}$ for comparisons by treatment).

The substantial average improvement seen in patients who received IVIG was virtually identical to that for patients who received the placebo infusion (Figure 1). Most of the improvement occurred within the first 6 months, as the mean increase in LVEF from baseline was 14 ± 13 EF units at 6 months and 15 ± 14 EF units at 12 months. No effect of treatment was evident (increase in LVEF at 6 months: IVIG = 0.14 ± 0.12 , placebo 0.14 ± 0.14 ; 12 months: IVIG = 0.16 ± 0.12 , placebo 0.15 ± 0.16).

Functional Capacity

Among patients with data at baseline and 12 months ($n = 48$), peak oxygen consumption (peak $\dot{V}O_2$) as assessed by metabolic stress testing increased significantly over time from 20.2 ± 5.7 mL \cdot kg⁻¹ \cdot min⁻¹ at baseline to 23.0 ± 7.1 mL \cdot kg⁻¹ \cdot min⁻¹ at 1 year ($P < 0.001$). No effect of therapy on improvement in functional capacity was evident (peak $\dot{V}O_2$ at baseline: IVIG 20.0 ± 5.9 , placebo 20.4 ± 5.6 ; at 12 months: IVIG 22.5 ± 6.5 , placebo 23.7 ± 7.8 ; $P = \text{NS}$ for effect of therapy on improvements over time). Examination of 6-minute walk data ($n = 42$) demonstrated that functional improvement occurred as early as 1 month and peaked by 6 months (distance walked within 6 minutes in meters: baseline 386.4 ± 171.1 , 1 month 452.3 ± 162.1 , 6 months 498.0 ± 178.0 , and 12 months 493.5 ± 179.2 ; $P < 0.001$ for test of change over time, no treatment effect evident in subset analysis).

Event-Free Survival

A total of 9 patients had secondary events during follow-up, including 6 IVIG patients (3 deaths, 2 transplants, and 1 LVAD placement with subsequent transplant) and 3 patients assigned to placebo (1 death, 1 transplant, and 1 LVAD placement). Patients without events were followed up for a median of 23 months (range 14 to 41 months). The overall event rate was low, with a 1-year Kaplan-Meier event-free survival rate of 91.9% and a 2-year rate of 88.4%. No significant difference in event-free survival was seen by treatment ($P = 0.39$ for comparison of event-free survival by log-rank test).

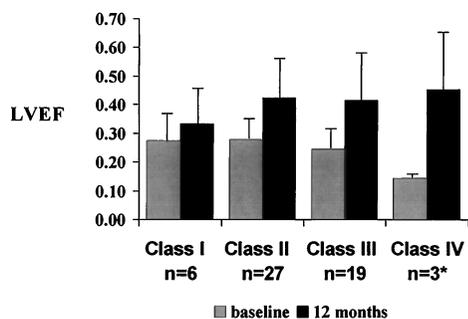


Figure 2. LVEF at baseline and 12 months after randomization by NYHA class at presentation. Patients with baseline and 12-month multigated acquisition scan data only. Higher NYHA functional class at entry was significantly associated with lower LVEF at baseline ($P=0.02$), but there was a nonsignificant trend toward higher LVEF at 12 months. *Another NYHA class IV patient, excluded from this analysis because baseline LVEF (0.30) was determined by ventricular angiography, had LVEF of 0.69 at 1 year after randomization.

Predictor of Outcome by Baseline Parameters

NYHA Class at Entry

Thirty-four patients were NYHA class I or II at entry, whereas 28 were class III or IV. Higher NYHA class at entry was associated with lower baseline LVEF ($P=0.02$) but a trend toward higher LVEF at 1 year (Figure 2). In part, this may represent a “survivor effect,” because of the 6 patients who died or received a transplant during the first year, all but 1 were class NYHA III or IV at presentation (percentage of patients alive and event-free at 1-year follow-up for NYHA class I, II, III, and IV was 100%, 96%, 86%, and 67%, respectively).

Endomyocardial Biopsy

Two (20%) of 10 patients with cellular inflammation on endomyocardial biopsy had events during the first year versus 4 (8%) of 52 of those with negative biopsies. Histological findings on biopsy (the presence or absence of cellular inflammation, fibrosis, or hypertrophy) also did not predict subsequent improvements in LVEF (Table 2). Of patients

TABLE 2. Baseline and 12-Month LVEF and Change in LVEF Over Time, According to Biopsy Status

	Baseline LVEF	12-Month LVEF	Change Over Time
Cellular inflammation at biopsy			
Absent (n=52)	0.25±0.09	0.41±0.14	0.15±0.14
Present (n=10)	0.25±0.08	0.49±0.19	0.21±0.14
Fibrosis at biopsy			
Absent (n=23)	0.26±0.08	0.43±0.13	0.16±0.12
Present (n=39)	0.25±0.09	0.41±0.15	0.15±0.15
Hypertrophy at biopsy			
Absent (n=31)	0.26±0.09	0.44±0.14	0.17±0.14
Present (n=31)	0.24±0.08	0.40±0.15	0.13±0.14

No statistically significant differences were found between subgroups with respect to these outcomes.

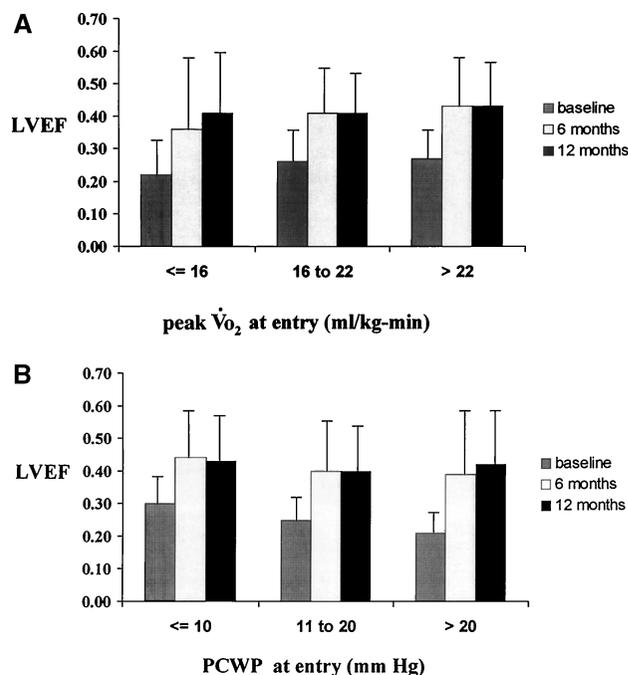


Figure 3. A, LVEF at baseline, 6 months, and 12 months by tertiles of functional capacity by metabolic stress testing (peak $\dot{V}O_2$) at time of entry. Peak $\dot{V}O_2$ at entry was not associated with LVEF at baseline or at 6 or 12 months after randomization ($P=NS$). B, LVEF at baseline, 6 months, and 12 months by tertiles of PCWP at time of entry. Higher PCWP at entry was associated with lower LVEF at baseline ($P<0.001$), but no differences were noted at 6 or 12 months ($P=NS$).

whose LVEF normalized (≥ 0.50) at 1 year, 16 of 20 had biopsies that were negative for cellular inflammation. The overall increase in LVEF at 12 months was 0.21 ± 0.14 in patients with cellular inflammation and 0.15 ± 0.14 among those with negative biopsies ($P=0.27$).

Hemodynamic Assessment and Functional Testing

Baseline hemodynamic assessment (pulmonary capillary wedge pressure [PCWP]) and metabolic stress testing (peak $\dot{V}O_2$) did not correlate with either 12-month LVEF ($r=-0.18$ and 0.02 , respectively; $P=NS$) or change from baseline to 12 months ($r=0.04$ and -0.04 , respectively; $P=NS$). In a similar fashion, examination of tertiles of peak $\dot{V}O_2$ (Figure 3A) or PCWP (Figure 3B) did not suggest any predictive value with respect to subsequent LV recovery.

Discussion

Despite the potential therapeutic efficacy suggested by previous uncontrolled studies, treatment of adult patients with recent-onset cardiomyopathy with immune globulin in this placebo-controlled trial did not affect improvements in LVEF or functional capacity during follow-up. Although the mean improvement in EF at 1 year of 16 EF units in the treated group was similar to that seen in the previous pilot study, this increase was essentially equaled by patients who were given placebo. This high rate of spontaneous recovery with conventional therapy was greater than anticipated but most likely underlies the apparent improvement reported in previous uncontrolled reports.

The overall improvement in LVEF for the entire IMAC study population exceeded that seen in the Myocarditis Treatment Trial,⁴ the largest randomized and placebo-controlled trial testing the effects of immunosuppression (prednisone and cyclosporine) in patients with presumed myocarditis. Our study population differed from the Myocarditis Treatment Trial in that only 10 of 62 patients had cellular inflammation on their endomyocardial biopsy, and 7 were classified as having myocarditis (or borderline) by the Dallas criteria.¹³ However, our data also suggest that the improvements in EF were similar in patients with and without cellular inflammation. Therefore, the difference in biopsy status is unlikely to explain the difference between the improvement seen in the present study and the previous trial. A more important distinction may be the duration of symptoms. All patients in the present study had <6 months of symptoms, whereas those in the Myocarditis Treatment Trial could have a history of heart failure for up to 2 years before randomization.

Previous retrospective studies have also shown significant improvements in LVEF for patients with recent-onset dilated cardiomyopathy. Dec et al,⁹ more than a decade ago, found that one third of patients with acute dilated cardiomyopathy (defined as <6 months of symptoms) had improvement of ≥ 10 EF units on follow-up. Similarly, a review of patients with dilated cardiomyopathy referred to the University of California at Los Angeles for cardiac transplant evaluation within 6 months of onset found that 29% had an improvement of ≥ 15 EF units.¹⁰ By comparison, 31 (56%) of 55 IMAC patients had improvement of ≥ 10 EF units noted by 12-month follow-up, and 20 (36%) of 56 evaluated at 1 year achieved a final EF of ≥ 0.50 , essentially normalizing their ventricular systolic function.

The 2 previous studies^{9,10} of recent-onset cardiomyopathy predated the use of β -adrenergic antagonists in patients with heart failure.¹⁴ Therefore, the improved natural history of acute dilated cardiomyopathy suggested by the present study may be attributed in part to the emerging role of these agents in the management of patients with systolic dysfunction. Indeed, although only 18% of the IMAC population were given β -blockers at baseline, this proportion increased to 45% by the 12-month postrandomization visit.

Although advances in conventional medical therapy have improved outcomes for patients with new-onset dilated cardiomyopathy, its origin remains elusive. The low prevalence of myocarditis on biopsy in this group of patients with presumed myocarditis is consistent with previous studies.⁴ Although endomyocardial biopsy remains the "gold standard" for the diagnosis of myocarditis, sampling error and variability in histological interpretation markedly limit its sensitivity and diagnostic utility. Histology did not predict outcomes for the IMAC patients. Indeed, 75% (16/20) of those patients who normalized their LVEF during follow-up had biopsies at entry that were negative for cellular inflammation. Many of these patients likely did have transient myocardial inflammation despite their negative histology, and better methodologies are needed to more accurately diagnose such patients at the time of presentation.

The present study cannot address the use of immune globulin for the treatment of myocarditis and new-onset dilated cardiomyopathies in children. In the previous pediatric study,⁶ this illness in children was more frequently associated with a positive endomyocardial biopsy, febrile illness, and a short duration of symptoms, measured in days to weeks rather than months. Children appear more likely than adults to present in the earlier inflammatory stage of the illness, and animal studies of the effects of immune globulin on virally induced cardiomyopathy show the drug is most effective when given during the early viremic phase.^{15,16} Thus, failure of the IMAC study to prove efficacy for IVIG in the adult population does not rule out the potential effectiveness of immune globulin in children with a similar but potentially pathologically distinct disorder. However, our results do suggest that a prospective randomized study may be warranted in children to truly evaluate the potential efficacy of immune globulin in the pediatric population.

The dosing schedule of a single administration of 2 g/kg IVIG evaluated in the present study was based on its use in Kawasaki disease and myocarditis disorders in children,^{5,6} as well as initial pilot studies.^{7,8} When immune globulin is given as high-dose intravenous therapy, IgG levels generally return to baseline after 30 days, and when used as an immune modulating agent for chronic disorders, monthly infusions are occasionally utilized. The present study does not evaluate the potential effectiveness of a more prolonged dosing schedule. In addition, the magnitude of improvement for the control group was significantly greater than anticipated, and this may have limited the power of the study to detect subtler treatment differences.

The present study did not demonstrate evidence of therapeutic efficacy for immune globulin administration for adults with recent onset of dilated cardiomyopathy. However, treatment with standard therapies resulted in marked improvements in ventricular function in the majority of patients and normalization in one third. Although we were unable to demonstrate a beneficial therapeutic role for immune globulin, these overall outcomes should give clinicians further cause for optimism in the management of patients with this traditionally devastating disorder.

Appendix

Centers and investigators participating in the Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) trial: *University of Pittsburgh Medical Center*: D.M. McNamara, W.D. Rosenblum, R.J. Alvarez, Jr, G.A. MacGowan, S. Murali, A.M. Feldman, A.J. Demetris, F. Villanueva, K. Janosko, T. Tokarczyk; *Cleveland Clinic Foundation*: R. Starling, K. Kiefer; *Massachusetts General Hospital*: G.W. Dec, M.J. Semigran, T. DiSalvo, D. Cocca-Spofford; *Baylor Methodist Hospital*: G. Torre-Amione, M. Vooletich; *Hospital of the University of Pennsylvania*: E. Loh, D. DeNofrio, A. Kao, K. Craig, F. Pickering; *Mount Sinai Medical Center*: A. Gass, J. Alexis; *Data and Safety Analysis: University of Pittsburgh Graduate School of Public Health and Johns Hopkins School of Medicine*: R. Holubkov, P. Kessler.

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