γ-Globulin Treatment of Acute Myocarditis in the Pediatric Population

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Background Myocardial damage in myocarditis is mediated, in part, by immunological mechanisms. High-dose intravenous γ-globulin (IVIG) is an immunomodulatory agent that is beneficial in myocarditis secondary to Kawasaki disease, as well as in murine myocarditis. Since 1990, the routine management of presumed acute myocarditis at Children’s Hospital, Boston, and Children’s Hospital, Los Angeles, has included administration of high-dose IVIG.

Methods and Results We treated 21 consecutive children presenting with presumed acute myocarditis with IVIG, 2 g/kg, over 24 hours, in addition to anticongestive therapies. A comparison group comprised 25 recent historical control patients meeting identical eligibility criteria but not receiving IVIG therapy. Left ventricular function was assessed during five time intervals: 0 to 7 days, 1 to 3 weeks, 3 to 6 months, 3 to 6 months, and 6 to 12 months. At presentation, the IVIG and non-IVIG groups had comparable left ventricular enlargement and poor fractional shortening. Compared with the non-IVIG group, those treated with IVIG had a smaller mean adjusted left ventricular end-diastolic dimension and higher fractional shortening in the periods from 3 to 6 months (P=.008 and P=.033, respectively) and 6 to 12 months (P=.072 and P=.029, respectively). When adjusting for age, biopsy status, intravenous inotropic agents, and angiotensin-converting enzyme inhibitors, patients treated with IVIG were more likely to achieve normal left ventricular function during the first year after presentation (P=.03). By 1 year after presentation, the probability of survival tended to be higher among IVIG-treated patients (.84 versus .60, P=.069). We observed no adverse effects of IVIG administration.

Conclusions These data suggest that use of high-dose IVIG for treatment of acute myocarditis is associated with improved recovery of left ventricular function and with a tendency to better survival during the first year after presentation. (Circulation. 1994;89:252-257.)

Key Words • cardiomyopathy • myocardium • γ-globulin

Acute dilated cardiomyopathy can be caused by many different processes,1,2 of which myocarditis is among the most perplexing in its pathobiology and clinical course. Myocardial damage in myocarditis may be mediated by predominantly immunological mechanisms rather than by the direct effect of viral infection and replication. However, the efficacy of immunomodulatory regimens for treatment of viral-induced myocarditis remains controversial.3,4

High-dose intravenous γ-globulin (IVIG) has been effective in the treatment of a variety of immunologically mediated diseases.5-10 Recently, we described marked improvement in left ventricular contractility and myocardial function after IVIG treatment in children with myocarditis secondary to Kawasaki disease.11 Further supportive evidence for a beneficial effect of IVIG in myocarditis comes from a mouse model in which polyclonal immunoglobulin has been demonstrated to protect against myocardial damage.12

Since 1990, the management of presumed acute myocarditis at Children’s Hospital, Boston, and Children’s Hospital, Los Angeles, has included administration of high-dose IVIG in addition to conventional supportive therapies for congestive heart failure. The purpose of our retrospective study was to assess the effect of IVIG therapy in patients with presumed myocarditis on survival and recovery of left ventricular function.

Methods

Subjects We reviewed all consecutive cases of patients with acute congestive cardiomyopathy associated with left ventricular dysfunction verified by echocardiogram who presented to Children’s Hospital, Boston, and Children’s Hospital, Los Angeles, between January 1985 and December 1991. All patients presenting after 1990 received IVIG; patients first evaluated between 1985 and 1989 served as historical controls. Patients were selected according to the following criteria: acute (<3 months) onset of congestive heart failure and echocardiographic documentation of diminished left ventricular function. We excluded patients with evidence of long-standing dilated cardiomyopathy by history or physical examination; documentation of conditions known to be associated with acute congestive heart failure, eg, sepsis, metabolic disorder, toxic shock syndrome, HIV infection, Kawasaki disease, primary arrhythmia, or structural heart disease; previous treatment with a known cardiotoxic agent; family history of dilated cardiomyopathy; and evidence of any cause of acute dilated cardiomyopathy other than myocarditis by history, physical examination, or myocardial biopsy. The study was approved by each institution’s committee on clinical investigation.
Normal subjects whose data were used to derive z scores of echocardiographic parameters included 256 children who were free of known cardiovascular disease, were taking no cardioactive medications, and had normal results from physical examinations, ECGs, and intracardiac anatomy by two-dimensional echocardiography.

Echocardiography

Data were collected by previously reported methods. The primary echocardiographic outcome measures for this study were end-diastolic dimension and fractional shortening. Left ventricular end-diastolic dimension was measured at the time of maximum left ventricular dimension. The left ventricular percent fractional shortening was calculated as the difference between the dimensions at end diastole and end systole divided by end-diastolic dimension. We assessed recovery of left ventricular function during the following five time periods after presentation: 0 to 7 days (39 patients), 1 to 3 weeks (30 patients), 3 weeks to 3 months (25 patients), 3 to 6 months (19 patients), and 6 to 12 months (21 patients). If more than one echocardiogram was performed in any given time interval, the earliest study was used for analysis. Children less than 2 years old usually received sedation with chloral hydrate; however, the physical state of patients during echocardiography (eg, postprandial) was not recorded.

Endomyocardial Biopsy

All endomyocardial biopsies were reviewed by a designated cardiac pathologist at each center. Of the 39 patients in whom a biopsy was obtained, only two patients had a repeat biopsy. Usually five to seven endomyocardial biopsy specimens were obtained from each child during catheterization. The samples, generally 1 mm in diameter, were fixed in 10% formaldehyde for conventional light microscopy or immediately fixed in 2.5% glutaraldehyde for electron microscopy. One piece was embedded in OCT and kept frozen at −70°F. All diagnostic interpretations were made after examination of routine histological slides, plastic-embedded sections, and electron microscopy. A definitive diagnosis of myocarditis was made in the presence of a lymphocytic infiltrate associated with myocyte degeneration or necrosis. The extent of myocardial damage varied from a single focus to multiple foci of myocyte degeneration or necrosis. Patients whose biopsies showed myocyte hypertrophy or interstitial fibrosis indicative of chronic disease were excluded from the present study. We classified a myocardial biopsy as "positive" if it met the Dallas criteria for "borderline" (with increased interstitial lymphocytes) or definitive myocarditis. Immunohistochernistry, immunoperoxidase staining, and polymerase chain reaction studies on biopsy material were not routinely obtained in this retrospective study.

Treatment

IVIG (Immuno AG, Vienna) was administered initially in a total dose of 2 g/kg over a maximum of 24 hours. In 4 of the 26 patients (15.4%), the IVIG group and additional dose of 1 g/kg was administered 1 week after the initial infusion. Other therapies for congestive heart failure, including inotropic agents, digoxin, diuretics, and afterload-reducing agents, were administered according to the routine practices of each institution. Fifteen of the 26 patients (57%) at Children’s Hospital, Boston, and 6 of 20 patients (30%) at Children’s Hospital, Los Angeles, received IVIG, reflecting the proportion of patients at each institution presenting in the period from 1990 to 1991.

Statistical Analysis

Primary outcomes for this study included survival and recovery of left ventricular function. For continuous variables, we used two-sample t tests to compare the treatment groups at baseline and within each study period. We used the χ² test to compare discrete data. Echocardiographic parameters were adjusted for body surface area (end-diastolic dimension) or for age (fractional shortening) using the z score method, in which the z score is calculated as (patient value minus population mean) divided by population standard deviation. We used t tests to compare the mean values of z-score–adjusted fractional shortening and end-diastolic dimensions to the normative mean of 0. Differences between groups were generally considered statistically significant at P=.05; however, to adjust for multiple t testing for differences in end-diastolic dimension and fractional shortening using the Bonferroni method, the cutoff for statistical significance was .01.

We compared the γ-globulin and conventional therapy groups with respect to survival and recovery of left ventricular function through 1 year after presentation. The differential follow-up periods of children in the treatment groups (10.5±2.1 versus 20.5±3.8 months, respectively; P=.029) precluded valid comparisons beyond this point.

The Kaplan-Meier method was used to obtain survival estimates. We did not distinguish between death and cardiac transplantation. We compared point estimates of survival between groups at two predetermined time points: 6 months and 1 year after presentation. We also compared the entire survival experience using the log rank test. We used the Cox proportional hazards method to compare the survival experience of the two treatment groups, adjusting for potential confounding variables such as age, biopsy status, or treatment with intravenous inotropic agents or angiotensin-converting enzyme (ACE) inhibitors.

We defined left ventricular function as "recovered" when the fractional shortening was within 2 SD of the normal mean for age. We used an approach identical to that described for survival analyses to compare groups with respect to recovery of left ventricular function. Statistical analyses were performed with Statistical Analysis Systems (Cary, NC).

Results

Of the 46 children with acute myocarditis, 21 (45.7%) were treated with high-dose IVIG and 25 (54.3%) were recent historical control patients who did not receive IVIG therapy. All patients received anti congestive therapies. The patient characteristics of the two groups are summarized in Table 1. Children in the two groups did not differ significantly in sex distribution, age at presentation, time from onset of symptoms to hospital admission, percent with a myocardial biopsy positive for acute myocarditis, or indexes of illness severity, including initial left ventricular end-diastolic dimension, fractional shortening, pulmonary capillary wedge pressure, lowest pH, lowest serum bicarbonate, or cardiac index. However, patients receiving IVIG therapy were more likely to have received treatment with intravenous afterload-reducing agents (P<.001) and inotropic agents (P<.01) as well as with ACE inhibitors after hospital discharge (P=.021).

Five patients (10.9%) were treated with prednisone, of whom three were in the non-IVIG group and two in the IVIG group. Two patients (both in the non-IVIG group) who received prednisone were also treated with cyclosporine. Among the three patients in the non-IVIG group, one died, one underwent cardiac transplantation, and one had persistent ventricular dysfunction. Both patients in the IVIG group showed normalization of left ventricular function.

Although survival tended to be better among IVIG-treated patients, the difference in the overall survival experience did not achieve statistical significance in our small sample (P>.10; Fig 1). Six months after presentation, the probability of survival among IVIG-treated...
TABLE 1. Comparability at Baseline for Conventional Therapy With and Without IVIG

<table>
<thead>
<tr>
<th></th>
<th>IVIG</th>
<th>No IVIG</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;2 y*</td>
<td>16/21</td>
<td>14/25</td>
<td>NS</td>
</tr>
<tr>
<td>Male*</td>
<td>10/21</td>
<td>14/25</td>
<td>NS</td>
</tr>
<tr>
<td>Positive biopsy*</td>
<td>12/19</td>
<td>8/20</td>
<td>NS</td>
</tr>
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<td>Captopril/enalapril treatment*</td>
<td>15/17</td>
<td>10/19</td>
<td>.02</td>
</tr>
<tr>
<td>Intravenous inotropes*</td>
<td>10/21</td>
<td>13/25</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Intravenous afterload*</td>
<td>15/21</td>
<td>5/25</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mm Hgt</td>
<td>14.3±1.94</td>
<td>18.4±3.25</td>
<td>NS</td>
</tr>
<tr>
<td>Lowest pH†</td>
<td>7.22±0.37</td>
<td>7.30±0.31</td>
<td>NS</td>
</tr>
<tr>
<td>Lowest serum bicarbonate†</td>
<td>13.5±1.5</td>
<td>17.3±1.17</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index‡</td>
<td>3.10±0.35</td>
<td>3.39±0.32</td>
<td>NS</td>
</tr>
<tr>
<td>Time from symptoms to admisison, d (median, interquartile range)</td>
<td>2</td>
<td>4.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

IVIG indicates intravenous γ-globulin.
*Values are no. of patients (%).
†Values are mean±SEM.

patients compared with those treated only with conventional therapy was .84 versus .69 (P<.10); by 12 months, the probability of survival tended to be higher among IVIG-treated patients (.84 versus .60, P=.069). We investigated potentially confounding variables (young age, biopsy positivity, treatment with ACE inhibitors) individually and in combination using Cox proportional hazards models. The survival estimates were similar after adjusting for these variables.

We explored the effect of IVIG treatment on left ventricular end-diastolic dimension (Fig 2 and Table 2) and on fractional shortening. End-diastolic dimension was z-score adjusted for body surface area, with a higher z score indicating a larger ventricle. At baseline, the end-diastolic dimension of both groups was more dilated than normal (P<.001); patients who received IVIG did not differ significantly from those treated with conventional therapy. Compared with patients who did not receive IVIG, those treated with IVIG had a smaller mean adjusted left ventricular end-diastolic dimension in the intervals from 3 to 6 months (P=.008) and from 6 to 12 months (P=.072) after presentation. Patients treated with conventional therapy continued to have a mean end-diastolic dimension significantly (P<.01) larger than normal in all periods of comparison within the first year after presentation, whereas the mean end-diastolic dimension of children treated with IVIG was not significantly different from normative values after 3 months.

Fractional shortening was z-score adjusted for age, with lower z scores reflecting poorer ventricular function (Fig 3 and Table 2). At presentation, all patients had severely depressed left ventricular function. Fractional shortening in both groups improved progressively over the first year; children treated with IVIG had a higher fractional shortening than those treated with conventional therapy alone in the time intervals from 3 to 6 months (P=.033) and from 6 to 12 months (P=.029). By 6 to 12 months, mean adjusted fractional shortening in the γ-globulin group was not significantly different from normative values (z=−1.01, P>.10), whereas that of children who did not receive IVIG remained significantly depressed (z=−5.51, P<.001).

The overall probability of left ventricular function recovering to normal during the first year after presentation tended to be higher among patients who received IVIG therapy (P=.06; Fig 4). By 6 months after presentation, the probability of recovery of left ventricular function among children who received IVIG was significantly greater than among those who did not.

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Kaplan-Meier estimates of survival among patients treated with intravenous γ-globulin (IVIG) or without intravenous γ-globulin (No IVIG). Each step represents death or cardiac transplant. The vertical lines represent 95% confidence intervals around the point estimates of probability of survival at 6 and 12 months.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Plot of left ventricular end-diastolic dimension, z score adjusted for body surface area, according to time after presentation with presumed acute myocarditis. The solid horizontal line and shaded area represent the expected population mean±2 SD, encompassing the values of 95% of the normal population. Solid circles and vertical lines depict the mean and 95% confidence limits (CL) for adjusted end-diastolic dimension in patients treated with intravenous γ-globulin (IVIG) for each time period since presentation. Open circles and vertical lines represent the mean and 95% CL for the group that did not receive γ-globulin therapy (No IVIG).
function among IVIG-treated patients compared with those in the conventional therapy group was .48 versus .26 (P>.10); by 12 months after presentation, these probabilities were 1.00 versus .37 (P<.001).

To assess whether the beneficial effect of IVIG on recovery of left ventricular function could be confounded by age, biopsy status, or use of ACE inhibitors, we adjusted for these variables individually and in combination using the Cox proportional hazards model. When adjusted for biopsy status alone, IVIG was not a significant predictor of recovery of left ventricular function. However, when adjusted for age alone, IVIG was associated with superior recovery of left ventricular function in the IVIG group was significantly better (P=.02 and P=.05, respectively). Similarly, adjustment for long-term treatment with ACE inhibitors did not influence the beneficial effect of IVIG on recovery of left ventricular function (P=.013). Finally, when simultaneously adjusting for age, biopsy status, intravenous inotropic agents, and ACE inhibitors, IVIG significantly influenced the course of recovery of left ventricular function (P=.03).

We observed no adverse effects of IVIG administration. A dose of 2 g/kg required a 40-mL/kg volume infusion within 24 hours, but we could not detect any exacerbation of congestive heart failure in these patients. Our ability to discern worsening congestive heart failure may have been limited as anticongestive therapy had already been instituted in all patients. No patients had hypotension or symptoms suggestive of anaphylaxis.

**Discussion**

In this retrospective study of IVIG treatment of presumed acute myocarditis in children, treatment with IVIG was associated with superior recovery of left ventricular function in multivariate models adjusting for age, biopsy status, and use of inotropic agents and ACE inhibitors. γ-Globulin administration was also associated with a trend toward improved survival 1 year after presentation. We observed no adverse effects of IVIG administration.

![Fig 3. Plot of fractional shortening, z-score adjusted for age, according to time after presentation with presumed acute myocarditis. The solid horizontal line and shaded area represent the expected population mean±2 SD, encompassing the values of 95% of the normal population. Solid circles and vertical lines depict the mean and 95% confidence limits (CL) for adjusted fractional shortening in patients treated with intravenous γ-globulin (IVIG) for each time period since presentation. Open circles and vertical lines represent the mean and 95% CL for the group that did not receive γ-globulin (No IVIG).](image)

![Fig 4. Kaplan-Meier estimates of recovery of left ventricular function among patients treated with intravenous γ-globulin (IVIG) or without intravenous γ-globulin (No IVIG). Each step represents recovery of left ventricular function, defined as a z-score-adjusted fractional shortening of more than −2. The vertical lines represent 95% confidence intervals around the point estimates of probability of recovery at 6 and 12 months.](image)
Acute myocarditis may be initiated by viral infection, but subsequent myocardial damage appears to be mediated by autoimmune mechanisms in addition to direct viral infection.\textsuperscript{15} The use of immunosuppressive agents for treatment of acute myocarditis is controversial\textsuperscript{16-18}; both beneficial and deleterious effects have been noted.\textsuperscript{16-18} Parillo et al\textsuperscript{16} found an initial improvement in ventricular function in patients with dilated cardiomyopathy who received steroids compared with control subjects who received conventional therapy; however, there was no significant difference in ventricular function between the two groups 6 months after presentation. Treatment of children with biopsy-positive myocarditis with prednisone was found to have a beneficial effect on outcome.\textsuperscript{18} Animal studies have almost uniformly shown that treatment with steroids during the viral replication phase (3 to 5 days after virus injection) enhances myocardial damage,\textsuperscript{19} whereas steroid treatment decreases myocardial necrosis if treatment is delayed until the phase of lymphocytic infiltration.\textsuperscript{20-23}

A murine model supports the premise that IVIG therapy for myocarditis is beneficial.\textsuperscript{12} Weller et al\textsuperscript{12} explored whether treatment with mouse polyclonal immunoglobulin would prevent cardiac inflammation in Balb/c male mice infected intraperitoneally with coxsackievirus B3. Animals treated with mouse immunoglobulin 2 days before infection showed $>50\%$ reduction in myocarditis compared with animals treated with phosphate-buffered saline, human immunoglobulin, or monoclonal mouse immunoglobulin G to an extraneous antigen. Mouse polyclonal immunoglobulin also minimized myocardial damage when given 24 or 48 hours after infection.

In clinical studies in humans, IVIG has been shown to accelerate recovery of myocardial function in myocarditis associated with Kawasaki disease.\textsuperscript{11} Myocarditis is a nearly universal feature of acute Kawasaki disease, and abnormalities of left ventricular systolic function may persist after resolution of clinical and laboratory indexes of systemic inflammation.\textsuperscript{24} Histological findings include interstitial myocarditis during the acute phase of the disease\textsuperscript{25} as well as hypertrophy of myocytes and fibrosis on late biopsy.\textsuperscript{26} Mean fractional shortening among patients treated with aspirin alone reached the normal range only beyond 1 year after disease onset. In contrast, mean fractional shortening in IVIG-treated patients was normal by 11 to 31 days after disease onset.\textsuperscript{11}

The mechanism by which IVIG may improve myocardial dysfunction in myocarditis is unknown. IVIG could be effective by providing specific antibodies to viruses and thus could lead to a more rapid clearing of myocardial viral infection. However, in the murine model of coxsackievirus myocarditis, the pooled mouse immunoglobulin often contained no neutralizing antibody to coxsackievirus yet was effective.\textsuperscript{12} An alternative mechanism of $\gamma$-globulin's action may be modulation of the immune response,\textsuperscript{27} leading to decreased cardiac inflammation or to downregulation of proinflammatory cytokines that have direct negative inotropic effects.\textsuperscript{28-30} It appears that the negative inotropic effects result from the generation of nitric oxide induced by various cytokines.\textsuperscript{31} In engaging the low-affinity $F_\gamma$ receptors, IVIG induces synthesis of the interleukin-1 receptor antagonist, and this may result in the downregulation of nitric oxide synthase.\textsuperscript{31} We did not test the use of IVIG in patients with known long-standing cardiomyopathy, but its potential mechanisms of action would suggest greatest usefulness during the acute inflammatory process. The IVIG product that we used is an intact, unmodified preparation that appeared to cause very few adverse effects. There are insufficient published data to compare the efficacy of commercially available IVIG preparations.

These data on the use of $\gamma$-globulin in acute myocarditis should be viewed as preliminary in view of several limitations in our study. Our patient selection and exclusion criteria attempted to maximize the percent of patients with acute myocarditis in the study sample, but discrimination of acute myocarditis from the acute presentation of a cardiomyopathy was necessarily inexact. Acute and convalescent viral titers were not systematically obtained in this retrospective study, and repeat endomyocardial biopsies that might have yielded additional supportive evidence of acute myocarditis were not performed in children for ethical reasons. Data on hospital course and subsequent outcome were collected retrospectively and thus are subject to the problems of incomplete and inconsistent recording. In analyzing the change in left ventricular function over time, not all patients were studied in all time periods, allowing for the possibility of selection bias. Patients who received $\gamma$-globulin were compared with recent historical controls; although the patient groups appeared to be comparable at baseline and we adjusted for known confounders (eg, ACE inhibitors), other aspects of patient care may have changed over time. Furthermore, the initiating agents for acute myocarditis and subsequent clinical course may differ from year to year and by geographic location. Finally, the relatively small number of patients in our study limits our ability to assess the extent to which confounding factors may contribute to the association between $\gamma$-globulin treatment and improved recovery of left ventricular function as well as the extent to which this association is subject to effect modification.

In summary, these data suggest that use of high-dose IVIG for treatment of acute myocarditis may be associated with improved recovery of left ventricular function and with a tendency toward better survival during the first year after presentation. Prospective, randomized, clinical studies are needed to elucidate the effects of IVIG treatment during the acute stage of myocarditis on ultimate outcomes.

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