Randomized, Placebo-Controlled Study for Immunosuppressive Treatment of Inflammatory Dilated Cardiomyopathy
Two-Year Follow-Up Results
Romuald Wojnicz, MD; Ewa Nowalany-Kozielska, MD; Celina Wojciechowska, MD; Grażyna Ghanowska, MD; Przemysław Wilczewski, MD; Tomasz Niklewski, MD; Marian Zembala, MD, PhD; Lech Polonowski, MD, PhD; Marius M. Rozek, MD; Jan Wodniecki, MD, PhD

Background—Previous studies have shown disappointing results for immunosuppressive treatment in patients with dilated cardiomyopathy. Therefore, we studied the effectiveness of such therapy in patients with HLA upregulation on biopsy.

Methods and Results—Of 202 patients with dilated cardiomyopathy, 84 patients with increased HLA expression were randomized to receive either immunosuppression or placebo for 3 months; they were then followed for 2 years. After 2 years, there were no significant differences in the primary end point (a composite of death, heart transplantation, and hospital readmission) between the 2 study groups (22.8% for the immunosuppression group and 20.5% for the placebo). The secondary efficacy end point included changes in ejection fraction, end-diastolic diameter, end-diastolic volume, end-systolic volume and NYHA class; left ventricular ejection fraction increased significantly in the immunosuppression group compared with the placebo group (95% CI, 4.20 to 13.12; \( P = 0.001 \)) after 3 months of follow-up. The early favorable effects of immunosuppressive therapy on left ventricular volume, left ventricular diastolic dimension, and New York Heart Association class were also present. This improvement was maintained in the immunosuppression group at 2 years (ejection fraction: 95% CI, 6.94 to 19.04; \( P < 0.001 \)). In addition, on the basis of the protocol-specified definition of improvement, 71.8% patients in the immunosuppression group versus 20.9% patients in the placebo group met the criteria of improvement after 3 months (\( P < 0.001 \)). At the end of the follow-up period, 71.4% patients from the immunosuppression group versus 30.8% patients from the placebo group were improved (\( P < 0.001 \)).

Conclusions—These data demonstrate a long-term benefit of immunosuppressive therapy in patients with dilated cardiomyopathy and HLA upregulation on biopsy specimens. Thus, restoration of immunosuppressive therapy for such patients should be considered. (Circulation. 2001;104:39-45.)

Key Words: cardiomyopathy ▪ myocarditis ▪ heart failure ▪ immunohistochemistry ▪ HLA antigens

Dilated cardiomyopathy is not a single disease but a heterogeneous group of disorders that includes idiopathic, immune, and specific cardiomyopathy.1 Myocarditis, regardless of its pathogenesis, is thought to be a main cause of dilated cardiomyopathy.2 Unfortunately, the onset of disease may be asymptomatic, and its first manifestation is often heart failure.3,4 Although in many cases, the cause of myocarditis remains unknown, numerous factors can cause myocardial inflammation, including infections, toxic injuries, etc.5 Although some patients with myocarditis recover spontaneously and completely, a few may progress into chronic inflammatory heart disease, which presents clinically in many cases as inflammatory dilated cardiomyopathy.6,7

See p 4

The diagnosis of myocarditis is based on histopathological criteria defined by the presence of inflammatory cellular infiltration and myocardial necrosis.8 The diagnosis is hampered by the focal nature of the disease and, despite multiple biopsies, sampling error still occurs.9,10 Although the Dallas criteria are an invaluable aid in myocarditis diagnosis, they are only as good as a specimen allows and they are often not sensitive enough to make an accurate diagnosis. Moreover, histology alone cannot readily distinguish between different forms of the disease, such as acute or chronic autoimmune myocarditis.10,11 Unlike histological features of myocarditis, which tend to be focal, immunohistological markers of...
months in association with an ejection fraction (EF) ≤ 40%.

The treatment of myocarditis is still problematic, and attempts to treat it with nonselective anti-inflammatory therapy remain controversial. Because the first randomized trial of immunosuppressive treatment for idiopathic dilated cardiomyopathy by Parrillo and coworkers, which was based on clinical enrollment for treatment, did not find that such therapy was efficacious, we tried to find new criteria that would enable us to select patients with inflammatory dilated cardiomyopathy who were potentially better responders for such therapy than those randomized previously. We hypothesized that the qualification of patients for immunosuppressive treatment should be based on an immunohistological evaluation of an endomyocardial biopsy instead of a clinical and/or histopathological diagnosis. Accordingly, in this prospective, randomized study, we used the increased expression of HLA in cardiac biopsy specimens to select patients for treatment. Thus, we studied 84 patients with immunohistologically verified chronic myocarditis who were randomly selected for treatment with or without immunosuppression in addition to conventional therapy.

Methods

Patient Enrollment

Enrollment took place from January 15, 1995, through October 30, 1997. The study population consisted of 202 patients with chronic heart failure due to dilated cardiomyopathy. All of them underwent endomyocardial biopsies. Eighty-four patients with the strong expression of HLA in biopsy specimens were randomized to placebo or immunosuppressive therapy. Among them, 31 patients with a history of ischemic heart disease or ≥ 2 standard risk factors for atherosclerosis underwent coronary angiography. Chronic heart failure was defined as dyspnea or fatigue at rest or exertion for ≥ 6 months in association with an ejection fraction (EF) ≤ 40%. The EF was assessed by echocardiography and radionuclide ventriculography.

Clinical characteristics of the patients are summarized in Table 1. The main exclusion criterion was lack of increased expression of HLA molecules in the biopsy. The remaining exclusion criteria included recent (<6 months) onset of systolic heart failure, all known causes of heart failure (such as hypertension, significant coronary artery disease, valvular heart disease [but not relative mitral regurgitation], endocrine disease, significant renal disease, drug or alcohol abuse, and therapy with steroids within 6 months before the study). The baseline clinical assessment included physical examination, ECG, 24-hour ECG monitoring, echocardiography, radionuclide ventriculography, and coronary angiography.

The local human studies committee of the Silesian School of Medicine, Katowice, Poland, approved the protocol. Written informed consent was obtained from all study patients.

Therapy

All patients received conventional therapy, which included digitalis, diuretics (furosemide 40 to 80 mg/d and spironolactone 100 mg/d), an ACE inhibitor (captopril 50 to 75 mg/d), β-blockers (metoprolol tartrate [Metocard], 50 to 100 mg/d), nitrates, an antiarrhythmic drug (amiodarone hydrochloride [Cordarone], 200 to 400 mg/d), and bed rest. Patients were randomized to placebo or immunosuppressive therapy with steroids and azathioprine added to conventional therapy. Prednisone was started at a dose of 1 mg · kg⁻¹ · d⁻¹. After 12 days, the dose was tapered off every 5 days by 5 mg/d until reaching the maintenance dose of 0.2 mg · kg⁻¹ · d⁻¹ for a total of 90 days. Azathioprine was given at a dose of 1 mg · kg⁻¹ · d⁻¹ for a total of 100 days.

Noninvasive Evaluation

Complete M-mode, 2D, and Doppler echocardiographic examinations were performed with a 2.5 MHz transducer using a Hewlett-Packard SONOS 1000. EF was calculated in a standard manner and was used to assess left ventricular systolic function. Left ventricular end-diastolic diameter (EDD, mm) was measured from the M-mode recordings, as recommended by the American Society of Echocardiography. Left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) were obtained from the apical 4- and 2-chamber views by the modified Simpson’s method. Echocardiograms (on-line and off-line) were assessed by 2 experienced investigators independently (interobserver variability was <8%). Final assessment was made by consensus. In addition, EF by echocardiography was verified by radionuclide ventriculography with technetium-99 m. The New York Heart Association (NYHA) class was used to assess functional capacity.

Invasive Evaluation and Endomyocardial Biopsy

Patients with suspected coronary artery disease underwent coronary angiography. Patients with any significant lesion (>50% stenosis) were excluded from this study. A right ventricular endomyocardial biopsy was performed using a Cordis biopette. A minimum of 5 specimens were obtained. Routinely, 4 specimens were used for histological evaluation and 2 were used for immunohistology. Tissue for immunohistochemistry, after embedding in medium (OCT compound, Miles Inc.), was snap-frozen in liquid nitrogen. Histopathological evaluation of biopsy specimens was performed according to the Dallas criteria. This evaluation was not taken into account for therapeutic decision-making.

Immunohistological Study

Acetone-fixed frozen sections (5 μm thick) were incubated with mouse monoclonal anti-human antibodies (HLA-ABC [clone W6/32; MHC class I] and HLA-DR, α chain [clone TAL.IB5; MHC class II]) from DAKO. HLA-DR antibodies were diluted 1:200, but HLA-ABC were diluted 1:400 in Tris-buffered saline (pH 7.6). The streptavidin-biotin method (DAKO LSAB+ Kit/alkaline Phosphatase Detection system/New Fuchsin Substrate System) was used according to the manufacturer’s instructions. The primary antibody was omitted from negative control slides. As a positive control, liver biopsy specimens from patients with chronic active hepatitis were used. The immunohistological examination of biopsy specimens was made by 2 investigators independently; each was blinded to clinical features and histopathological diagnosis. The interobserver variabili-

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo Group (n=43)</th>
<th>IT Group (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (95% CI)</td>
<td>39 (29, 60)</td>
<td>41 (16, 61)</td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>6/37</td>
<td>9/32</td>
</tr>
<tr>
<td>EF, %</td>
<td>24.9±7.3</td>
<td>23.8±8.6</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>14 (32.5)</td>
<td>11 (26.8)</td>
</tr>
<tr>
<td>NYHA functional class, II/III/IV</td>
<td>15/26/2</td>
<td>6/29/4</td>
</tr>
<tr>
<td>Systolic BP, mm Hg (95% CI)</td>
<td>127 (110, 146)</td>
<td>131 (105, 139)</td>
</tr>
<tr>
<td>Dallas criteria of MCI, n (%)</td>
<td>Active</td>
<td>3 (7.0)</td>
</tr>
<tr>
<td></td>
<td>Borderline</td>
<td>6 (13.9)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>34 (79.1)</td>
</tr>
<tr>
<td>Dropouts after 2 y, n (%)</td>
<td>3 (7.0)</td>
<td>4 (9.3)</td>
</tr>
</tbody>
</table>

IT indicates immunosuppressive therapy.
ity was <2%. Each specimen was evaluated qualitatively (intensity of staining) and semiquantitatively (scoring system). The semiquantitative scoring system was defined previously. For the purposes of this study, staining ≥2 of one or both classes of HLA was considered positive.

Follow-Up, End Points, and Definition of Improvement

The effectiveness of therapy was assessed at the times for follow-up (3, 6, 12, and 24 months) after the treatment. The 2-year follow-up was designed for final assessment of long-term treatment efficacy. Cardiac death, heart transplantation, and readmission to the hospital constituted the composite primary efficacy end point. The predefined, secondary efficacy end point included changes in EF, EDD, EDV, and ESV and changes in NYHA score, analyzed separately.

In addition to end point efficacy, patients were classified as improved if they met an increase of ≥5 percentage points in the absolute EF and had ≥2 selected criteria, such as decrease of EDV, ESV, or EDD ≥10% and 1 class decrease in NYHA class compared with baseline measures.

Statistics

The number of patients enrolled in this 2-center trial was based on the results of previous studies on a related subject. The baseline characteristics of the treated groups were compared by Student’s t test for continuous variables and the Mann-Whitney U test or Fisher’s exact test for categorical data. Normally distributed data are described with mean and SD, but non-normally distributed data are presented as median and interquartile range.

Changes in the primary and secondary end points were analyzed in the following 2 ways. (1) An intention-to-treat analysis with the 2-tailed Fisher’s exact test included all randomized patients (except patients who withdrew) for all follow-up end points. This test was also used to compare the proportions of patients who improved, as defined by the protocol. Patients who died, underwent heart transplantation, and/or were readmitted to the hospital were classified as unimproved. (2) A carry-forward analysis excluded patients who were lost to follow-up and who achieved the primary end point, and data were analyzed by Student’s t test for between-group comparisons and by 2-way (group effect and time effect) repeated measures ANOVA. In addition, for group comparisons in terms of changes in the values of measures (EF, EDV, ESV, EDD, and NYHA score), a Mann-Whitney U test and median test were used. This comparison was made only for patients who completed the 2-year follow-up period. Death and heart transplantation were also analyzed by log-rank test for event-free survival analysis. Statistical significance was accepted at the 95% confidence interval (P<0.05). Statistical analysis was made using SPSS version 9.01 software.

Figure 1. A, Diffusely distributed strong expression of HLA class I antigens localized on microvascular endothelium (arrows) and other interstitial cells only. Magnification ×400. B, Strong expression of HLA class I antigens with concomitant multifocal induction of these antigens on cardiac myocytes (arrows) near the areas of inflammatory infiltration (arrowhead). Magnification ×400. C, Increased expression of HLA class II antigens found on endothelial and other interstitial cells (arrows). Magnification ×400. D, Focally distributed, weak HLA class II antigen staining is present on some microvascular endothelial cells (arrows). Magnification ×400.

Figure 2. Serial EF in 58 patients from placebo (n=30) and immunosuppression groups (n=28) who completed 2 years of follow-up. ● and lines show mean±SD.
Follow-Up and Primary Efficacy End Point

Two patients from the immunosuppression group did not complete the treatment and were lost to follow-up. None of the remaining patients achieved the primary end point at 3 months. After 6 months, 4 patients (2 patients in both groups) were lost to follow-up. The primary end point was less common in patients in the immunosuppression group compared with those in the placebo group (2 versus 5 cases), but this difference was not statistically significant. After 1 year, 4 more patients withdrew from the study (2 patients in both groups). At this time, the primary end point occurred in 4 of the 33 patients from the immunosuppression group (12.1%) and 3 of the 39 patients in the placebo group (7.7%). At 2 years, the primary end point occurred in 2 of 35 patients (5.7%) from the immunosuppression group and none of those in the placebo group. The immunosuppression and placebo groups did not differ significantly in the primary efficacy end point at the end of follow-up (8 of 35, 22.8% for immunosuppression versus 8 of 39, 20.5% for placebo; P=NS by log-rank test for event-free survival analysis).

Secondary Efficacy End Point

Results are displayed for the secondary end point in Table 2 and Figure 2. No significant difference was noted in baseline values, although there was a trend for higher ventricular volumes among the placebo group. Immunosuppressive therapy was associated with significant early improvement. By the carry-forward analysis, mean EF increased significantly in the immunosuppression group compared with the placebo group (95% CI, 4.2 to 13.1; P<0.001). Secondary end points for left ventricular volumes and EDD decreased significantly in the immunosuppression group. The favorable effect of immunosuppressive therapy on NYHA class was also present, but it was not statistically significant (P=0.097). The increase in the mean EF achieved by month 3 was maintained in the immunosuppression group compared with the placebo group after 6 months of follow-up (95% CI, 3.8 to 14.8; P=0.001).

EDV, ESV, and EDD (like EF) improved at the time of second follow-up, as shown in Table 2. A shift in the distribution of patients from greater to lesser severity of heart failure was noted. In patients with NYHA class II at baseline, a significant decrease in EF occurred (P=0.001). In patients with NYHA class III at baseline, an increase in EF occurred (P=0.001), but it was not statistically significant. After 1 year, 4 more patients withdrew from the study (2 patients in each group). The primary end point occurred in 4 of the 33 patients from the immunosuppression group (12.1%) and 3 of the 39 patients in the placebo group (7.7%). At 2 years, the primary end point occurred in 2 of 35 patients (5.7%) from the immunosuppression group and none of those in the placebo group. The immunosuppression and placebo groups did not differ significantly in the primary efficacy end point at the end of follow-up (8 of 35, 22.8% for immunosuppression versus 8 of 39, 20.5% for placebo; P=NS by log-rank test for event-free survival analysis).
failure in the immunosuppression group was found, but this difference was not statistically significant \( (P=0.063) \). The carry-forward analysis revealed further amplification of the benefit in the immunosuppression-treated patients at 1 year. In relation to baseline data, mean EF increased significantly in the immunosuppression group compared with the placebo group (95% CI, 5.5 to 17.7; \( P<0.001 \)). In addition, EDV, ESV, and EDD improved significantly in the immunosuppression group. However, there was no difference in NYHA functional class between the studied groups \( (P=0.165) \). The improvement found in previous follow-up in the immunosuppression group compared with the placebo group was maintained at 2 years. A consistent, significant increase in mean EF in the immunosuppression group was noted (95% CI, 6.9 to 19; \( P<0.001 \); Figure 2). The remaining secondary efficacy end points were also significantly different and favored immunosuppression-treated patients. Immunosuppressive therapy was also associated with long-term significant improvement in NYHA functional class \( (P=0.005; \text{Table 2}) \).

**Clinical Outcomes Based on the Protocol-Specified Definition of Improvement**

The forecasted early and long-term benefits of immunosuppression among patients with immunohistologically diagnosed myocarditis are substantial. On the basis of the protocol-specified definition, 28 of 40 patients (71.8%) in the immunosuppression group versus 9 of 43 patients (20.9%) in the placebo group met the criteria of improvement \( (P=0.001) \). At 3 months. After 6 months, such improvement was found in 30 of 37 patients (81.1%) from the immunosuppression group compared with 10 of 41 patients (24.4%) from the placebo \( (P<0.001) \). Similarly, 24 of 35 patients (68.6%) from the immunosuppression group and 11 of 39 patients (28.2%) from the placebo group improved after 1 year of follow-up \( (P=0.001) \). The clinical improvement by intention-to-treat analysis found at the previous follow-up was also observed at year 2 in 25 of 35 patients (71.4%) from the immunosuppression group and 12 of 39 patients (30.8%) from the placebo group \( (P=0.001) \). Interestingly, at the 2-year follow-up among nonrandomized, immunohistologically negative patients, protocol-defined improvement was present in 23 of 53 subjects (43.4%).

**Adverse Drug Effects**

During immunosuppressive therapy, side effects were observed in 16 of 41 patients (39%). The increased body weight (>5 kg) due to steroids after 90 days of therapy was present in 14 of 41 patients (34%) in the immunosuppression group. Two of 41 patients (4.9%) developed hypertension at the time of immunosuppressive treatment.

**Discussion**

Our results have shown, for the first time, that short-term immunosuppressive therapy with steroids and azathioprine may provide long-term benefit in patients with chronic heart failure and immunohistologically proven myocarditis, presented here as an upregulation of HLA on biopsy specimens. Our study was based on the assumption that myocarditis is, at least in part, an immunological disorder and that immunosuppressive treatment will be successful if ongoing inflammation is detectable by immunohistochemistry. It seems that if patients are selected for immunosuppression on the basis of the upregulation and induction of HLA on biopsy specimens, immunosuppressive therapy may significantly improve clinical status. Therefore, we postulate that qualification for this approach should be based on immunohistochemistry instead of histopathological diagnosis or clinical suspicion of myocarditis. These data did not show, however, that immunosuppressive therapy yielded a better survival rate than conventional therapy. This observation is in accord with previous studies on a related subject. \(^{15,19}\) Accordingly, it may be postulated that causes of fatal cardiac events are related, at

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**TABLE 2. Continued**

<table>
<thead>
<tr>
<th>1-Year Follow-Up</th>
<th>2-Year Follow-Up</th>
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<tbody>
<tr>
<td>( n )</td>
<td>Mean±SD</td>
</tr>
<tr>
<td>30</td>
<td>31.5±12.9</td>
</tr>
<tr>
<td>28</td>
<td>43.1±10.0</td>
</tr>
<tr>
<td>30</td>
<td>204.7±72.6</td>
</tr>
<tr>
<td>28</td>
<td>150.9±57.9</td>
</tr>
<tr>
<td>30</td>
<td>148.4±67.0</td>
</tr>
<tr>
<td>28</td>
<td>101.0±45.5</td>
</tr>
<tr>
<td>30</td>
<td>62.9±9.9</td>
</tr>
<tr>
<td>28</td>
<td>55.2±9.9</td>
</tr>
<tr>
<td>30</td>
<td>2.0</td>
</tr>
<tr>
<td>28</td>
<td>1.0</td>
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</tbody>
</table>

IT indicates immunosuppressive therapy; LV, left ventricular.
least in part, to the advance of the disease rather than pathogenesis or treatment alone.

Immunohistochemistry has recently become useful in the detection of ongoing inflammation in the myocardium.11,20 Our previous study demonstrates that de novo induction of HLA may be the most appropriate immunohistological marker of ongoing inflammation in the myocardium.19 It is known that under physiological conditions, endothelial and other interstitial cells constitutively express low levels of HLA; however, cardiac myocytes do not share these characteristics under normal conditions.22 Specimens from patients with histologically active myocarditis demonstrate increased expression and myocyte induction of these molecules.23 It is worth emphasizing that this immunohistological hallmark of the specimens was also found in Chagas cardiomyopathy, which is postulated as a human model of chronic myocarditis.24

It seems that the immunological mechanisms are independent of clinical presentation of myocarditis and that the chronic inflammatory process has an autoimmunological component, regardless of the trigger mechanism initiating it.25 Because the final targets for immunosuppression are the same, it may be possible that short-term therapy could interrupt the autoimmune response in the myocardium.12 Moreover, the short duration of immunosuppression may also reduce the side effects of such therapy.26 Unlike current results, in the first randomized treatment trial conducted by Parrillo et al,15 there was no observed long-term benefit of steroid therapy in patients with idiopathic dilated cardiomyopathy. This discrepancy of remote outcome is due to study design differences between the trials. In Parrillo et al’s study,15 the entrance criteria were based on clinical status. Moreover, the immunosuppressive regimen consisted of steroids alone. In the present study, the design was based on HLA expression and induction in biopsy as the sole criterion for a patient’s randomization. Furthermore, we used a 2-component immunosuppressive regimen involving steroids and azathioprine. Interestingly, in the light of the present evidence, the final conclusion of Parrillo et al’s study15 that steroids should not be used as a standard therapy for dilated cardiomyopathy is still topical.

Active myocarditis (as based on Dallas criteria) was found in 8% of studied patients. In early reports, the prevalence of myocarditis in biopsies from patients with unexplained congestive heart failure ranged from 4% to 80%.27 These results show that a histopathological diagnosis of myocarditis based on these criteria is difficult because of the focal nature of the inflammatory lesions in the myocardium, which contributes to sampling error.28 Moreover, the pathogenic role of lymphocytes in the myocardium remains unclear because they do not necessarily reflect activated or cytotoxic cells.29 In relation to the facts noted above, the randomized study conducted by Masson at al17 failed to demonstrate the benefit of immunosuppressive therapy in patients with histopathologically proven myocarditis. When we used immunohistological criteria to detect myocarditis, the clinical outcome was different from that found by Masson et al17 but consistent with the results of the previous nonrandomized studies by Maisch et al26 and Kühl and Schultheis,30 which suggested a beneficial effect of immunosuppressive therapy in patients with immunohistologically proven myocarditis.

Although the study was not designed to examine immunohistologically negative patients, it is worth emphasized that 43% of nonrandomized, immunohistologically negative, and conventionally treated patients improved after 2 years compared with 30% of the randomized placebo patients. Such spontaneous improvement has been previously reported in patients with dilated cardiomyopathy and myocarditis.31 It may be hypothesized that in nonrandomized patients there was no true ongoing myocarditis, but only transient autoimmunity, which may respond better to conventional therapy.

Conclusions

Our data demonstrate a significant benefit of 2-component immunosuppression in patients with HLA upregulation on biopsy specimens. Considering the results, we propose restoring immunosuppressive therapy in patients with immunohistologically proven myocarditis. This treatment should be based on immunohistological examination of the biopsy specimens rather than histopathological diagnosis or clinical suspicion of the disease alone. In addition, because immunological markers of inflammation are distributed throughout the myocardium, this approach will likely lead to a lower incidence of false-negative diagnosis and it will significantly decrease the number of postbiopsy complications; hence, fewer specimens will be required.

Study Limitations

The present study may be limited by the exclusion of patients without increased expression of HLA on biopsy specimens from randomization. Only patients with HLA upregulation were selected for randomization. This approach was based on the results of previous studies that failed to demonstrate effectiveness of immunosuppressive therapy in clinically diagnosed idiopathic dilated cardiomyopathy and/or histopathologically verified myocarditis. However, a few nonrandomized studies demonstrated clinical benefit of immunosuppressive treatment in patients with immunohistologically proven myocarditis. Because steroid therapy is identifiable clinically by the development of cushingoid features, the assigned treatment was known during the trial.

Acknowledgments

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References


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