Inflammatory Cardiomyopathy (Myocarditis)

Which Patients Should Be Treated With Anti-Inflammatory Therapy?

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In patients presenting with congestive heart failure in the United States, approximately one-quarter have idiopathic dilated cardiomyopathy (IDC). IDC is thought to result from a number of mechanisms that injure the myocardium and lead to a common pathway of cardiac dilatation and heart failure. Known mechanisms of myocardial injury include alcohol, toxins, infections, cytotoxic chemotherapy, and metabolic abnormalities. Recent studies have highlighted important genetic links, suggesting that familial transmission is important in a subgroup of IDC patients. However, in most IDC patients, a cause cannot be determined.

Substantial animal experimental data has demonstrated a strong pathogenetic link between infectious agents (usually viruses) and subsequent immune-mediated damage to the myocardium resulting in IDC. Human studies have demonstrated a high prevalence of viral genome in the hearts of patients with IDC. Enteroviruses, adenovirus, influenza, HIV, and hepatitis C have been implicated in the pathogenesis of dilated cardiomyopathy and myocarditis. Much of the data suggests cell-mediated immune damage, although cytokines and antibodies have also been hypothesized to play a role.

Patients with heart failure due to IDC should be treated with conventional heart failure therapy, which includes diuretics, angiotensin-converting enzyme (ACE) inhibitors, digitalis, β-blockers, vasodilators, aldosterone antagonists, and other effective medications and technology. However, the specific question for patients with an inflammatory cardiomyopathy is whether a regimen designed to reduce or eliminate inflammation would provide additional clinical benefit compared with conventional heart failure therapy. This has been a difficult question to answer for several reasons. First, the clinical presentation of inflammatory cardiomyopathy is highly heterogeneous. Most patients with myocarditis are asymptomatic, and their condition often resolves spontaneously. Another group of myocarditis patients present with a fulminant course characterized by severe heart failure, cardiogenic shock, and a high death rate. Use of mechanical assist devices in this group has been associated with a favorable outcome, although some patients require heart transplantation. A less acute group of patients presents with moderate myocardial dysfunction and heart failure. In general, most studies have evaluated this latter clinical group.

Second, the diagnosis of inflammatory cardiomyopathy has been the subject of controversy. Clinical criteria are very general. The standard microscopic criteria (Dallas criteria) applied to endomyocardial biopsies were derived by consensus among a group of pathologists, and the criteria required both inflammatory cells and myocyte necrosis. Studies have demonstrated great variability (disagreement of 40%) among expert pathologists evaluating the same biopsies. Further, biopsies obtained from different parts of the right ventricle show focal infiltrates (spatial variability), and biopsies obtained at different time points document intermittent inflammatory infiltrates (temporal variability). Thus, the endomyocardial biopsy using conventional histological criteria has many diagnostic shortcomings, and it cannot be considered a gold standard of diagnosis.

Third, a substantial number of patients with myocarditis will improve their clinical status and ventricular performance during follow-up. Therefore, one must include an adequate control group to evaluate a therapy’s effect.

Fourth, it is not clear when an anti-inflammatory therapy should be initiated. Two observations are most likely to have a therapeutic effect in the early acute stage when neutrophils predominate; in the subacute stage with lymphocytes and macrophages; or in the subacute/chronic stage with macrophages and fibroblasts? Although one might argue for early intervention, acute myocarditis may resolve and improve spontaneously. Thus, patients with persistent ventricular dysfunction and chronic inflammatory biopsies may comprise a more appropriate population in which to institute therapy.

Although a number of observational trials of myocarditis have been published, they do not provide meaningful data because control patients may improve spontaneously. Therefore, only controlled studies will be considered. Several randomized, controlled trials have been conducted evaluating an anti-inflammatory regimen in IDC and/or myocarditis. Parrillo et al10 studied 102 patients with dilated cardiomyopathy who had evidence of inflammation (n=60; reactive patients) or no evidence of inflammation (n=42; nonreactive patients). Reactive patients had one or more of the following criteria: fibroblastic (n=36) or lymphocytic (n=2) infiltration or immunoglobulin deposition (n=16) on endomyocardial biopsy, a positive gallium scan (n=7), or an elevated erythrocyte sedimentation rate (n=18). Nonreactive patients had none of these features.

Each group was given conventional heart failure medications. Reactive and nonreactive groups were separately ran-
domized to prednisone or no prednisone (control) therapy. The prospectively defined end point was an increase in left ventricular ejection fraction (LVEF) by $\geq 5\%$. At 3 months, 67\% of reactive patients who received prednisone had improved compared with 28\% of the reactive control group ($P=0.004$). The reactive prednisone group increased their LVEF by $5.5 \pm 2.0\%$, and the reactive control group increased LVEF by $2.3 \pm 2.4\%$ ($P=0.035$). The nonreactive patients did not improve with prednisone.

In a subgroup of reactive patients (those with any cellular infiltrate on endomyocardial biopsy), prednisone improved both LVEF and treadmill exercise duration. In most of the patients in the reactive group, the cellular infiltrate on biopsy consisted of fibroblasts with some lymphocytes and macrophages. Thus, most of these patients had subacute or chronic myocarditis.

At 3 months, the patient regimen was changed from daily prednisone to alternate day prednisone. On this alternative-day regimen, the prednisone-induced improvement in LVEF in the reactive patients was no longer present at 9 months from study initiation. The study was not statistically powered to evaluate survival; however, no difference in mortality was seen.

The authors concluded that daily prednisone produces an improvement in LVEF in reactive patients with IDC. However, the increases in LVEF were modest. In patients with chronic inflammation (largely fibroblasts) on biopsy, both LVEF and exercise tolerance were improved by prednisone. This study suggested that certain subpopulations of IDC patients may respond favorably to prednisone, but the broadly identified “reactive” group was probably too heterogeneous to produce a substantial response to therapy.

A second controlled trial by Mason et al$^5$ randomized 111 patients diagnosed by Dallas criteria (lymphocyte infiltration and myocyte necrosis) to an immunosuppressive regimen (prednisone and cyclosporin or azathioprine) versus control. The prospectively defined end point was LVEF at 6 and 12 months. Both the immunosuppressive and control groups demonstrated an increase in LVEF at 6 and 12 months, with no difference between the groups. If one uses a 5\% increase in LVEF as a definition of improvement (the prospective criteria used by Parrillo et al$^{10}$), the immunosuppressive group had more patients demonstrate an improved LVEF than the control group. Although this study was not powered to evaluate survival, no difference was seen in mortality between the control and immunosuppressive group.

The trial by Mason et al$^5$ had 2 limitations. (1) Only 78 of 111 patients were followed for the entire 12 months, so 30\% of patients were lost to follow-up. (2) The pathological (Dallas) criteria used presented problems. When a panel of expert cardiac pathologists reviewed the biopsy slides on the 111 patients, the experts disagreed with the original diagnosis of myocarditis in 39\% of the study patients. This highlights the significant problems surrounding pathological diagnosis by conventional histopathology.$^9$:

Another recent controlled trial randomized 62 patients to therapy with immune globulin or control. The primary end point was change in EF at 12 months. No treatment effect was seen, although both groups had a 14\% increase in LVEF.$^{11}$

These randomized controlled trials, especially the trial by Parrillo et al$^{10}$ conducted in patients with severe ventricular dysfunction (baseline LVEF 17\%) and chronic histological changes on biopsy, suggest that some patients with IDC will have a favorable ventricular performance improvement with anti-inflammatory therapy. The studies raise the important question of how to identify a subgroup of “responsive” IDC patients.

In the present issue of *Circulation*, Wojnicz and colleagues$^{12}$ report the 2-year follow-up results from a randomized, placebo-controlled study of immunosuppressive treatment for IDC. The authors used immunohistochemistry technology on endomyocardial biopsy specimens to identify proteins upregulated by human leukocyte antigen (HLA).$^{13}$ HLA genes and proteins represent the human major histocompatibility complex, a series of genes, proteins, and other gene products whose major function is to regulate the immune response to an allograft in transplantation. Identification of these HLA proteins on the surface of cells has been associated with autoimmune reactions.$^{14}$ The authors reasoned that the presence of HLA antigens in the myocardium (myocytes, endothelial cells, and/or interstitial cells) would identify a relatively homogeneous population of patients with inflammatory cardiomyopathy due to active immune processes.

The authors screened 202 patients with unexplained chronic heart failure due to dilated cardiomyopathy. Patients with acute heart failure (<6 months) were excluded. Endomyocardial biopsy showed HLA positivity in 84 patients, and these were randomized to immunosuppression (with prednisone and azathioprine) or placebo for 3 months and follow-up for 2 years. After 2 years, the primary end point (a composite of death, heart transplantation or hospital readmission) did not differ between the study groups. However, the immunosuppressed patients demonstrated impressive increases in LVEF at 3 months and 2 years that were significantly different from controls. Similar improvements were also evident at 2 years in New York Heart Association (NYHA) functional class. The authors conclude that their study demonstrates the long-term (2 year) benefits of immunosuppressive therapy for patients with inflammatory cardiomyopathy, as defined by biopsy evidence of HLA upregulation. They argue that immunosuppressive therapy should be reconsidered as a possibly effective therapy in inflammatory cardiomyopathy.

Wojnicz and colleagues$^{12}$ are to be congratulated for conducting an excellent clinical trial. Their study significantly advances our understanding of the pathogenesis of inflammatory cardiomyopathy and its management. Although the primary end points were not different in the immunosuppressive and control groups, the secondary outcomes of improved ventricular function and NYHA class provide convincing evidence of a therapeutic effect of immunosuppressive therapy. Despite a relatively high dropout rate (31\% at 2 years), the serial data provide strong evidence of a beneficial effect of immunosuppression. Parrillo et al$^{10}$ showed an improvement in LVEF at 3 months in reactive patients receiving prednisone, and the Wojnicz study confirms the 3-month improvement and extends the findings to
include improved symptoms and ventricular performance at 2 years. Importantly, Wojnicz et al12 provide an HLA immunohistochemical methodology that identifies a more homogeneous population of responding patients with IDC.

In addition to the authors’ conclusion that immunosuppression has a beneficial effect on ventricular performance and NYHA class, the study suggests several other conclusions. First, in the 84 HLA-positive biopsies, Dallas criteria would have classified only 8% as active myocarditis, 19% as borderline myocarditis, and 73% as no myocarditis. This discrepancy emphasizes the inadequacy of the Dallas criteria as a clinically useful diagnostic method.

Second, Wojnicz et al12 randomized patients with heart failure lasting ≥6 months. Presumably, they thought that early (<6 months) onset heart failure was likely to be reversible and not in need of immunosuppressive therapy. Some previous trials studied largely early heart failure patients and noted a substantial improvement of LVEF in the control group. Patients with heart failure from IDC that has persisted for ≥6 months probably represent a more appropriate group to consider for immunosuppressive therapy.

Third, the study used prednisone and azathioprine for 3 months with 2 years of follow-up. Previous studies have used prednisone alone with daily and alternate day regimens,10 prednisone and cyclosporin8 (although a small subgroup received prednisone and azathioprine), and immune globulin.11 Some of the efficacy seen by Wojnicz et al12 may be due to their choice of an immunosuppressive regimen consisting of prednisone and azathioprine.

Finally, in my judgment, the most likely reason for Wojnicz et al’s12 success probably results from their selection criteria. They included patients with longstanding (≥6 months) IDC and with a positive endomyocardial biopsy for HLA antigens. Previous trials used conventional histological biopsy criteria that are insensitive and not specific for detecting persistent immune damage.

Cardiovascular disease treatment has seen many examples of therapies deemed ineffective until the development of an appropriate diagnostic method to select a responsive patient population. For example, in patients with myocardial infarction, thrombolytic therapy was deemed ineffective until it became clear that thrombolysis worked only in those patients with ST-segment elevation. In acute coronary syndromes, aggressive intervention works only in those with positive serum troponins and ST-segment depressions. Thus, it is likely that certain subsets of patients with inflammatory cardiomyopathy have persistent immune damage and will respond to immunosuppressive therapy. Wojnicz et al12 have provided convincing evidence that a positive biopsy for HLA antigen identifies a patient subgroup that has improvement in ventricular performance and NYHA class when given immunosuppressive therapy. Although cardiac function and functional class are important end points, I favor another larger, clinical trial that evaluates functional class, exercise tolerance, ventricular performance, and mortality with a longer follow-up period. Also, we need to work on standardizing the HLA immunohistological methods if they are to be employed widely.

Other tests of immune activation or damage should also be evaluated to develop even more specific markers to identify patients who may respond to immunosuppressive therapy. Wojnicz et al12 have provided the very important observation that certain populations of IDC patients have active immune damage, damage that can be identified by HLA immunohistochemistry and improved by immunosuppressive treatment. Our future task is to identify those responsive patient populations better.

References
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