Section 16: Myocarditis: Current Treatment

Overview

Myocarditis is a distinct clinical entity with a wide variety of cardiac manifestations including HF. Potential etiologies may include toxins, medications, physical agents and, most importantly, infections. The most common forms appear to be postviral in origin. The pathophysiology of myocarditis has been well established in animal models with myocardial damage due not only to direct infection, but also consequent to postinfectious, autoimmune-mediated myocardial inflammatory damage. In humans, ongoing myocardial inflammation may result in dilated cardiomyopathy, restrictive cardiomyopathy, or acute left ventricular (LV) failure without dilatation (fulminant myocarditis).

Myocarditis is histologically characterized by both an active inflammatory cellular infiltrate within the myocardium and associated myocyte necrosis (the Dallas pathologic criteria).[1] Although many clinicians and pathologists consider the Dallas criteria too restrictive, this classification has established uniform histologic criteria for diagnosis and has substantially reduced the wide variation in reported rates of this disease. Although the inflammatory infiltrate is lymphocytic in more than 90% of cases, eosinophilic infiltration or giant cell formation may occasionally be seen. The clinical features of myocarditis are extremely varied, ranging from asymptomatic electrocardiographic abnormalities observed during viral Coxsackie B outbreaks in the community to severe dilated cardiomyopathy with fulminant heart failure (HF) leading to transplantation or death.[2] Myocarditis may also cause ventricular arrhythmias or heart block or mimic acute myocardial infarction.[3,4] Both acute and chronic dilated cardiomyopathies may result from inflammatory heart disease. The histologic differentiation of myocarditis from idiopathic dilated cardiomyopathy remains problematic, because several published series suggest no difference in long-term prognosis, regardless of the presence or absence of myocardial inflammation.[5] Nonetheless, many clinicians believe that myocarditis is a potentially reversible form of cardiomyopathy and continue to perform endomyocardial biopsy searching for its presence.

Controversy continues to surround the best approach to the management of patients considered to have myocarditis. The following recommendation is based on a review of available data from uncontrolled and controlled evaluation of immunomodulatory therapy for the treatment of myocarditis.

Recommendation

16.1 Routine use of immunosuppressive therapies is not recommended for patients with myocarditis. (Strength of Evidence = A)

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Background

Uncontrolled Studies. More than 20 uncontrolled trials have been reported during the past 15 years on the use of immunosuppressive agents in the treatment of biopsy-proven lymphocytic myocarditis.[1] Therapies have included prednisone alone, prednisone and azathioprine, prednisone and cyclosporine, and short courses of OKT3. Virtually all immunosuppressive protocols can result in rapid histologic improvement or resolution of the inflammatory component of the disease. Unfortunately, little or no correlation exists between histologic improvement and ventriculographic improvement. Improvement in ventricular function has been reported to range from 0% to 100%.[1,6,7] Furthermore, spontaneous variation in LV ejection fraction (LVEF) and improvement in acute dilated cardiomyopathy are now well-recognized features of all forms of new onset cardiomyopathy. Thus uncontrolled series cannot answer the question as to whether the improvement in ventricular function exhibited by some patients was actually from treatment rather than spontaneous improvement in the disease itself.

Controlled Trials. Three randomized, placebo-controlled trials have been performed which examined the role of immunosuppressive therapy in the treatment of acute dilated cardiomyopathy or myocarditis. One study randomly assigned 102 patients with dilated cardiomyopathy to treatment with either prednisone (60 mg/day) or placebo for 3 months.[8] The trial concluded that prednisone had marginal clinical benefit and should not be administered as standard therapy for dilated cardiomyopathy patients. A major criticism of this trial was that only a small number of patients had histologically verified myocarditis. A second trial of 52 patients with recently diagnosed idiopathic dilated cardiomyopathy treated with either conventional therapy alone or in combination with prednisone reported an inflammatory response on endomyocardial biopsy in 23% of the overall population, 13% of whom had Dallas criteria myocarditis.[9] Immunosuppressed patients received 50 mg of prednisone daily for 2 weeks followed by a taper by 10 mg every 2 weeks until the drug was discontinued. Biopsy-documented myocarditis resolved in all patients within 3 months regardless of treatment modality. Survival at 24 months, the primary endpoint of the study, was 64 $\pm$ 12% for the prednisone-treated patients compared to 83 $\pm$ 8% for the untreated patients ($P = .57$). The presence of myocardial inflammation did not influence survival. Thus prednisone was determined to be ineffective in improving the primary end point in the study.

The Myocarditis Treatment Trial (MTT) examined immunosuppressive therapy consisting of prednisone and cyclosporine in 111 patients with histologically verified myocarditis and an LVEF $<45\%$ who were randomized to receive conventional therapy alone or combined with

immunosuppression for 6 months.[10] The primary outcome measure was prespecified as change in LVEF at 28 weeks. The majority of patients received prednisone and cyclosporine immunosuppressive treatment, because the azathioprine treatment limb was prematurely terminated from slow study enrollment. For the group as a whole, LVEF improved from 25% at baseline to 34% at 28 weeks. The mean change in EF did not differ between treatment groups. A higher LVEF at baseline, shorter duration of symptoms, but not the randomized treatment assigned, were positive independent predictors of improvement in EF at 28 weeks. There was no difference in survival between treatment groups; the mortality rate for the entire group was 20% at 1 year and 56% at 4.8 years. This study is the only sizable randomized trial specifically focused on treatment of patients with myocarditis. Unfortunately, prednisone and cyclosporine-based immunosuppressive therapy produced no clinical benefit.

High-dose gamma-globulin has been shown to be effective treatment for a variety of immunologically mediated diseases such as Kawasaki's disease. The use of intravenous immunoglobulin (2 g/kg) in 21 consecutive children treated for presumed acute myocarditis demonstrated a trend for improved survival in the immunoglobulin group compared to historical controls.[11] Small studies using intravenous immunoglobulin in adult patients have been negative.[12,13] All patients had New York Heart Association class class III or IV heart failure symptoms and an LVEF $<40\%$. One patient died, whereas the remaining 9 patients were discharged; EF in the survivors increased from 24% to 41%.

A prospective randomized multicenter trial of the use of immunoglobulin in patients with cardiomyopathy of less than 6 months duration and symptomatic HF submitted all patients to endomyocardial biopsy; however, only 16% of the 62 patients randomized had Dallas criteria myocarditis.[14] The immunoglobulin and placebo control population had identical survivals at one year (92% and 88% respectively), and increases in EF from 25% at baseline to 42% at the 12 month follow-up. Therefore, despite encouraging data from uncontrolled observations, immunoglobulin therapy does not provide benefit to patients with new-onset cardiomyopathy and myocarditis.

Increasing concerns have been raised concerning the ability to diagnose myocarditis by endomyocardial biopsy using the Dallas criteria exclusively. Of the 2233 patients considered candidates for inclusion in the MTT 2, only 214 were thought to have myocarditis as defined by the Dallas criteria. Of the 111 patients enrolled in the trial, only 64% were ''confirmed'' as having myocarditis after review by an expert panel of pathologists. Chow and Hauck performed serial myocardial biopsies on postmortem hearts of patients who had died of myocarditis.[15,16] Even with 5 biopsy samples, only two-thirds of patients studied would have had the diagnosis of myocarditis using the Dallas criteria. Others have demonstrated that even in the presence of viral RNA or DNA by polymerase chain reaction techniques, histologic myocarditis often is not confirmed.[17]

Two recent European investigators have added significantly to our understanding of histologic versus immunologic ''myocarditis.'' Wojnicz defined myocarditis by upregulation of human leukocyte antigen by endomyocardial biopsy in 84 patients of a cohort of 202 with new onset cardiomyopathy.[18] Patients were randomized prospectively to immunosuppression or placebo. Although the rates of death, transplantation, or hospitalization were virtually identical in the immunosuppressed and placebo-treated patients, those with immunosuppression increased their EF from 24% to 36%, whereas the control group showed virtually no increase. Based on the Dallas criteria alone, only 8.3% of the patients studied had active myocarditis and 19% had borderline myocarditis. Frustaci demonstrated histologic myocarditis in 112 of 652 patients with new-onset cardiomyopathy submitted to myocardial biopsy.[17] Of the 112 patients with myocarditis, 41 displayed progressive deterioration despite usual medical therapy and were treated with immunosuppression (azathioprine and prednisone). Approximately half of the patients responded to immunosuppressive therapy. Responders increased their EF from 26% to 47% and demonstrated healed myocarditis on follow-up biopsies. The 20 nonresponders had progressive deterioration to dilated cardiomyopathy, with 5 deaths and 3 cardiac transplantations. Cardiac antibodies were demonstrated in 90% of those who responded, compared with absence of antibodies in non-responders. The patients who failed to respond displayed viral persistence (85%).

Clearly, patients with subacute myocarditis and new onset dilated cardiomyopathy and HF often improve spontaneously with standard HF management. It is becoming increasingly clear that the Dallas criteria, which rely exclusively on histologic inflammatory infiltrate and myocyte necrosis, may be underestimating the presence of immune-related myocardial dysfunction. Recent evidence suggests that we may be on the verge of identifying patients for whom immunosuppressive therapy would be beneficial by using other markers of immune upregulation, anticardiac antibodies, or the absence of viral persistence. These data are not yet strong enough to alter our current recommendations, but should be revisited as new data become available.

Recommendation

16.2 Endomyocardial biopsy should be considered in patients with an acute deterioration of cardiac function of unknown etiology who are unresponsive to medical therapy.
(Strength of Evidence = B)

Background

There are distinct clinical pathologic forms of myocarditis in which endomyocardial biopsy establishes not only the diagnosis but prognosis and treatment options. These include fulminant myocarditis, giant cell myocarditis, chronic active myocarditis, and eosinophilic myocarditis, all of

which typically develop within 6 months of the onset of cardiomyopathy.

Fulminant myocarditis is characterized by an abrupt onset of profound HF within 1 month of a preceding clearly recognized viral illness.[19] Patients present with nondilated, thickened left ventricles with severe hypofunction on echocardiography. Endomyocardial biopsy reveals unquestionable histologic Dallas criteria myocarditis. These patients usually recover spontaneously within 2 weeks with complete resolution of histologic myocarditis and normalization of ventricular function. Their long-term prognosis is excellent. These patients should not be treated with immunosuppressive therapy.

Patients with giant cell myocarditis present with rapidly progressive HF, complete heart block, or malignant ventricular arrhythmias.[20] Many patients have an associated autoimmune process. Biopsy reveals widespread serpiginous necrosis and multifocal inflammation with eosinophiles, histiocytes, lymphocytes, and multinucleated giant cells. Patients with untreated giant cell myocarditis usually die within 3 months of presentation. There are preliminary data to suggest that high-dose immunosuppressive therapy may improve survival in this population.[21]

Patients with chronic active myocarditis have an indistinct onset.[22] They present with HF and mild LV dilation and systolic dysfunction. Endomyocardial biopsies reveal both ongoing active inflammation and fibrosis. Both processes progress over the course of the illness. Ultimately patients develop a restrictive cardiomyopathy with refractory HF, usually over 2 to 3 years.

Hypersensitivity to a number of standard drugs may result in an allergic myocarditis. This inflammation is characterized by peripheral eosinophilia and infiltration of the myocardium with lymphocytes, histocytes, and eosinophiles. This form of myocarditis is rarely recognized premortem and should be suspected in patients with stable LV dysfunction who deteriorate inexplicably, particularly after the initiation of a new medication.[23]

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