Intravenous Immune Globulin in the Therapy of Peripartum Cardiomyopathy

Biykem Bozkurt, MD,* Flordeliza S. Villaneuva, MD, FACC,† Richard Holubkov, PhD,‡ Tammy Tokarczyk, RN, BSN,† René J. Alvarez, Jr., MD, † Guy A. MacGowan, MB, BCH, † Srinivas Murali, MD, FACC, † Warren D. Rosenblum, MD, † Arthur M. Feldman, MD, PhD, FACC, † Dennis M. McNamara, MD, FACC†

Houston, Texas and Pittsburgh, Pennsylvania

OBJECTIVES We sought to evaluate the effect of therapy with intravenous immune globulin on recovery of left ventricular function in women presenting with peripartum cardiomyopathy.

BACKGROUND Peripartum cardiomyopathy is a rare complication of pregnancy that results in significant morbidity and mortality in women of childbearing age. Intravenous immune globulin has been reported to improve left ventricular systolic function in patients with acute dilated cardiomyopathy and myocarditis, but its effectiveness in peripartum cardiomyopathy is unknown.

METHODS In this retrospective study, we compared the clinical outcomes of six women with peripartum cardiomyopathy treated with intravenous immune globulin (2 g/kg) with those of 11 recent historical control subjects. All women in the study were referred between 1991 and 1998 with class II to IV heart failure and a left ventricular ejection fraction of 0.40. Left ventricular ejection was reassessed during early follow-up (6.1 ± 2.9 months).

RESULTS The two groups did not differ in terms of baseline left ventricular ejection fraction, left ventricular end-diastolic diameter, months to presentation, age or multiparity. The improvement in left ventricular ejection fraction in patients treated with immune globulin was significantly greater than in the conventionally treated group (increase of 26 ± 8 ejection fraction units vs. 13 ± 13, p = 0.042).

CONCLUSIONS In this small retrospective study of women with peripartum cardiomyopathy, patients treated with immune globulin had a greater improvement in ejection fraction during early follow-up than patients treated conventionally. Given the poor prognosis of women with peripartum cardiomyopathy who do not improve, this therapy merits further study. (J Am Coll Cardiol 1999;34:177–80) © 1999 by the American College of Cardiology

Peripartum cardiomyopathy is an uncommon complication of pregnancy occurring in 1:1,300 to 1:4,000 live births (1). This myocardial disorder classically presents in the last trimester or in the first few months postpartum (2) and is clinically indistinguishable from other forms of idiopathic dilated cardiomyopathy (3,4). Though its etiology remains unknown, most theories have focused on the hemodynamic (5,6) and immunologic stresses (7) of pregnancy. An immune pathogenesis is supported by the frequent finding of lymphocytic myocarditis on endomyocardial biopsy (8–11), and the fact that multiparity, or previous exposure to fetal or placental antigen, is a significant risk factor (2). In contrast to patients with idiopathic dilated cardiomyopathy, significant improvement in myocardial function is seen in 30% to 50% of patients in the first six months after presentation (12). However, for those patients who do not recover normal or near normal function, the prognosis is similar to other forms of dilated cardiomyopathy, with the overall rate of death or transplantation ranging from 29% to 43% (13,14).

Current therapeutic options consist of conventional supportive therapy for congestive heart failure (15,16). A single nonrandomized study (10) suggested immunosuppression may benefit women with biopsy-proven myocarditis. However, given the risks of immunosuppressive therapy, and the absence of a proven benefit in the myocarditis treatment trial (17), this therapy has not been widely utilized. In addition, the prevalence of myocarditis on biopsy series with peripartum cardiomyopathy ranges from 9% to 78% (10,11), and the role of immune modulatory therapy in the large percentage of women with negative biopsies remains unknown.

Intravenous immune globulin, a concentrated preparation of pooled polyclonal human antibodies (immunoglobulin
METHODS

Study subjects. Seventeen consecutive women with peripartum cardiomyopathy referred to the University of Pittsburgh Medical Center for evaluation between December 1991 and February 1998 were retrospectively identified. All patients presented with New York Heart Association class II to IV heart failure within the first six months postpartum with a left ventricular ejection fraction of <0.40, and were referred to the University of Pittsburgh Medical Center within the first year after delivery. All patients had an extensive cardiac evaluation to rule out other forms of cardiac disease.

Treatment group. The treatment group consisted of six women who presented between August of 1996 and February of 1998, and were treated with immune globulin in addition to conventional therapy. Immune globulin therapy consisted of 2 g/kg of immune globulin given as 1 g/kg q.d. intravenously on two consecutive days. Conventional therapy included angiotensin-converting enzyme inhibitors, digoxin and loop diuretics in all six patients. Only one patient was treated with a beta-adrenergic blocking agent. Two of six required inotropic therapy at the time of treatment, and one required intra-aortic balloon pump support.

Control group. The control group consisted of 11 women, 10 presenting before August of 1996, and one woman presenting after the initiation of investigations with immune globulin for whom therapy was recommended but was declined. Conventional therapy consisted of angiotensin-converting enzyme inhibitors in nine, digoxin in nine and beta-blockers in three. Two patients required inotropic support, and one required an intra-aortic balloon pump at the time of referral.

Assessment of left ventricular ejection fraction (LVEF). Baseline LVEF was measured by transthoracic echocardiography using modified Simpson's rule at the time of referral to the University of Pittsburgh Medical Center in 14 patients, and radionuclide angiography in three. One control patient died within the first week after presentation and was excluded from the follow-up analysis. In the remaining patients, LVEF was reassessed during the early follow-up at a mean of 6.1 ± 2.9 months (range 3 to 12). The time to follow-up assessment was similar for both groups (treatment 5.5 ± 2.4, control 6.4 ± 3.2 months). Left ventricular ejection fraction was reassessed using the same methodology as the baseline assessment for all but one patient.

Statistical analysis. Changes in LVEF over time were assessed using two-way repeated measures analysis of variance, with time being the within-subjects variable. Assessment of the effect of therapy over time was made by evaluating the interaction term in the model. Values are presented as mean ± standard deviation.

RESULTS

The clinical characteristics of the treatment group and control subjects are listed in Table 1. The treatment and control groups did not differ in age, degree of parity, months postpartum, left ventricular diastolic diameter or LVEF. Myocardial biopsies were performed in 11 of 17 total patients and revealed evidence of lymphocytic myocarditis in only one.

The change in LVEF from baseline to follow-up for both groups is depicted in Figure 1. The clinical outcomes of the control group are consistent with previous reports of the natural history of peripartum cardiomyopathy. Left ventricular ejection fraction improved at least 10 ejection fraction (EF) units in four of 11; however, only two achieved an LVEF >0.50, and four patients were either dead, or were left with severe left ventricular dysfunction. The mean improvement of ejection fraction for the 10 surviving control subjects was 13 ± 13 EF units.

The mean improvement of EF with immune globulin was 26 ± 8 EF units, significantly greater than in control subjects (p = 0.042 for the interaction of therapy and time; for the individual main effects, p < 0.001 for time and p = 0.69 for initial group assignment). All patients treated with immune globulin had an improvement in EF of at least 10 EF units and three had normalized their LVEF at the time of follow-up assessment. Only one patient was left with severe left ventricular dysfunction. This patient was referred late, seven months after her last pregnancy, required two inotropes at the time of therapy and subsequently required biventricular device support within one week of treatment.
with immune globulin. Of note, this patient’s ventricular function recovered sufficiently to allow discontinuation of biventricular device support. Right ventricular assist was discontinued within one week, and by 30 days there was echocardiographic evidence of left ventricular recovery. Left ventricular support was successfully removed two months later and this patient was discharged from the hospital on medical therapy and LVEF reassessed two months after device removal.

**DISCUSSION**

In the present study, the use of high dose immune globulin was associated with a marked improvement in LVEF during early follow-up, twice that seen in a recent historical control group. All but one patient in the treatment group achieved an ejection fraction >35% at six months, and these results closely parallel previously reported outcomes of treatment with immune globulin in children and adults with primary dilated cardiomyopathy and myocarditis. Given immune globulin’s effects as an immune-modulating agent, the apparent efficacy in the disorder supports the hypothesis that peripartum cardiomyopathy is driven by an autoimmune pathogenesis.

The majority of patients in this study had endomyocardial biopsies that were negative for cellular inflammation. This may imply that humoral factors, autoantibodies, cytokines or other anti-inflammatory mediators are more important in the pathogenesis of peripartum cardiomyopathy than cellular autoimmunity. However, sampling error and delays in presentation limit the sensitivity of endomyocardial biopsy, making interpretation of negative biopsies problematic. Conceivably cellular mechanisms may play a more significant role than was demonstrated by the current study.

**Immunologic changes of pregnancy.** Adaptive immunologic changes occur during pregnancy which allow maternal tolerance of paternal antigens in the developing fetus (21).
This includes the induction of suppressor cells that act to effectively suppress maternal rejection (22). These adaptive changes during pregnancy are associated with the clinical observation that autoimmune disorders such as rheumatoid arthritis and multiple sclerosis (23), which affect women during their reproductive years, tend to have lower relapse rates during pregnancy itself with a marked increase in the first few months postpartum. In a subset of women with recurrent spontaneous abortions, a defect in the suppression of maternal immunity has been postulated and immune globulin has been utilized to try to limit maternal rejection of the fetus (24).

Multiparity is a significant risk factor for elevations of antibodies directed against foreign human leukocyte antigens (25), demonstrating the importance of maternal–fetal interactions in this form of humoral immunity which complicates cardiac transplantation. High dose immune globulin has been shown to reduce the titer of autoantibodies in patients awaiting transplantation (26). Plasmapheresis has also been utilized effectively for this purpose (27), and may be an alternative to immune globulin therapy in peripartum cardiomyopathy. Recently a small controlled study of immunoadsorption in idiopathic dilated cardiomyopathy (28) demonstrated significant improvements in left ventricular function, suggesting that therapies directed against humoral autoimmunity may have a significant role in the treatment of this and related disorders.

Although the improvement seen in this retrospective analysis appears promising, the absence of a randomized control group limits our ability to draw firm conclusions about the efficacy of immune globulin without a larger multicenter controlled trial. The IMAC trial, a randomized prospective placebo-controlled trial of immune globulin in a related population of adult patients with myocarditis and recent onset idiopathic dilated cardiomyopathy, has completed the enrollment phase with outcome data available by late 1999. The results of this trial of immune globulin in a similar disorder may yield important insights in the potential use of this therapy in women with peripartum cardiomyopathy.

Reprint requests and correspondence: Dr. Dennis M. McNamara, University of Pittsburgh Medical Center, Division of Cardiology, 200 Lothrop St., S558 Scaife Hall, Pittsburgh, Pennsylvania 15213. E-mail: mcnamaradm@msx.upmc.edu.

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