Published by Elsevier Science Inc.

ISSN 0735-1097/03/$30.00

LETTERS TO THE EDITOR

Immunosuppressive Treatment in Familial Dilated Cardiomyopathy With Biopsy-proven Intramyocardial Inflammation?

In a recent issue of the *Journal*, Mahon et al. (1) added substantially to the pathogenesis of familial dilated cardiomyopathy (DCM), elucidating that intramyocardial inflammation, as assessed by immunohistochemical quantification of CD3+ T-lymphocytes and abundance of endothelial cell adhesion molecule expression (ICAM-1 and HLA-DR), is significantly present in asymptomatic individuals with left ventricular enlargement and who are relatives of patients with familial DCM. Their report confirms previous findings on anticardiac autoimmunity in familial DCM, such as autoantibodies (2) and the HLA type DR4-linked predisposition (3). The first successful immunosuppressive study in DCM, demonstrating beneficial long-term hemodynamic effects over a two-year follow-up period, was based on the immunohistochemical diagnosis of inflammatory cardiomyopathy (i.e., HLA abundance) (4). In contrast, preliminary data by Chimenti et al. (5) elucidated that only patients with biopsy-proven absence of viral persistence will benefit from such immunosuppressive treatment.

Given the reported absence of enteroviral, adenoviral, and cytomegaloviral genome in familial DCM (6), would the investigators consider immunosuppressive treatment to prevent disease progression in patients with established familial DCM and in their asymptomatic relatives who have left ventricular enlargement?

Michel Noutsias, MD
Department of Cardiology and Pneumonology
University Hospital Benjamin Franklin
Hindenburgdamm 30
D-12200 Berlin
Germany
E-mail: noutsias@zedat.fu-berlin.de

Matthias Pauschinger, MD
Uwe Kühl, PhD
Heinz-Peter Schultheiss, MD

PII S0735-1097(02)02673-6

REFERENCES

1. Mahon NG, Madden BP, Caforio ALP, et al. Immunohistologic evidence of myocardial disease in apparently healthy relatives of patients with dilated cardiomyopathy. J Am Coll Cardiol 2002;39:455–62.
2. Caforio ALP, Keeling PJ, Zachara E, et al. Evidence from family studies for autoimmunity in dilated cardiomyopathy. Lancet 1994;344: 773–7.
3. McKenna CJ, Codd MB, McCann HA, Sugrue DD. Idiopathic dilated cardiomyopathy: familial prevalence and HLA distribution. Heart 1997;77:549–52.
4. Wojnicz R, Nowalany-Kozielska E, Wojciechowska C, et al. Randomized, placebo-controlled study for immunosuppressive treatment of inflammatory dilated cardiomyopathy: two-year follow-up results. Circulation 2001;104:39–45.
5. Chimenti C, Calabrese F, Pieroni M, et al. Active lymphocytic myocarditis: virologic and immunologic profile of responders versus non-responders to immunosuppressive therapy (abstr). Circulation 2001;104:II559.
6. Mahon NG, Zal B, Arno G, et al. Absence of viral nucleic acids in early and late dilated cardiomyopathy. Heart 2001;86:687–92.

REPLY

We thank Dr. Noutsias and colleagues for their comments regarding our report (1). Although dilated cardiomyopathy (DCM) is classified as idiopathic, familial/genetic, viral and/or immune (2), in the real world we lack consensus diagnostic criteria for viral and/or immune DCM. In relation to the key question, as to whether immunosuppression is indicated in DCM patients and their relatives with left ventricular enlargement (LVE) (2), we would suggest that the rational base is the establishment of accepted consensus diagnostic criteria. This should set the groundwork for future controlled studies of immunosuppressive therapy in DCM. We agree with Dr. Noutsias and co-workers that autoimmune DCM is defined by lack of viral genome by polymerase chain reaction (PCR) and myocardial inflammation by immunohistochemistry. Although the study by Wojnicz et al. (3) has shown beneficial hemodynamic effects of immunosuppression after two-years, it failed to show a favorable effect on mortality, possibly because it was statistically underpowered. Conversely, the IMAC trial failed to demonstrate efficacy in recent-onset DCM and myocarditis, but patients were not stratified in terms of pathogenesis (4). Thus, multicenter studies enrolling adequate numbers of patients using consensus criteria for viral versus immune inflammation are needed. Meanwhile, on the basis of the Polish study (3) a short course of immunosuppression may be considered in patients with established inflammatory DCM, with no replicating virus. In these patients the prognosis remains poor, and the potential benefit of halting disease progression is high.

It is, however, premature to administer immunosuppression for asymptomatic LVE relatives with myocardial inflammation. Although such therapy has the potential to prevent disease progression, the absolute risk of progression in LVE needs to be quantified. Data from an initial cohort demonstrated progression in 27% of subjects over three years (5), but longer follow-up in a larger cohort is required. Second, five-year follow-up has revealed that serum detection of cardiac-specific antibodies (6) with or without LVE at baseline is also a noninvasive predictor of disease progression (7). The clinical challenge is to identify more accurately, ideally with noninvasive markers, asymptomatic relatives at risk. We believe it is necessary to obtain such data before considering a potentially deleterious therapy such as immunosuppression in asymptomatic relatives with preserved systolic function.

Alida L.P. Caforio, MD, PhD, FESC
Division of Cardiology
Department of Clinical and Experimental Medicine
Padua University Medical School
Policlinico Universitario
Centro "V. Gallucci"
via N. Giustiniani, 2
35128 Padua, Italy
E-mail: alida.caforio@unipd.it

Niall G. Mahon, MD
William J. McKenna, MD, FRCP, FACC, FESC

PII S0735-1097(02)02674-8