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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?

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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.

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Left Atrial Appendectomy and Maze

The feasibility and effectiveness of specific linear left atrial (LA) lesions to treat atrial fibrillation (AF) were addressed by Kottkamp et al. (1) in a recent issue of the *Journal*. Interestingly, linear lesions confined to the left atrium were able to cure AF in more than 90% of cases, and the technique was feasible with a minimally invasive right mini-thoracotomy approach. Although the main objective of AF cure is the restoration of sinus rhythm, it should be emphasized that the most dreadful consequence of the disease is embolic cerebrovascular accidents (CVA). Atrial fibrillation is responsible for 20% of all strokes, and the risk of stroke is increased fivefold in nonrheumatic AF and 17-fold in patients with mitral stenosis and AF (2).

The efficacy of systemic anticoagulation with warfarin to reduce the incidence of stroke has been demonstrated in randomized clinical trials, and the left atrial appendage (LAA) has been recognized as the source of more than 90% of emboli leading to CVA (3,4). Fifty percent of AF patients are age 75 or older, and it has been estimated that at least 20% have a contraindication to warfarin treatment (5). We believe that the importance of the LAA in the generation of embolic strokes should be addressed when a surgical approach to AF is contemplated and, therefore, we are concerned that the procedure proposed by Kottkamp et al. (1) may result in higher rate of CVA as compared to the classic maze approach, which includes LA appendectomy (6,7). It has been demonstrated that the maze procedure is associated with three-year 100% freedom from thromboembolic complications as compared to 83% in the non-maze group (8). In the study by Kottkamp et al. (1) surgical ablation was associated with restoration of sinus rhythm and an increase in LAA flow velocity that could potentially release occult clots into the systemic circulation. Moreover, oral anticoagulant therapy was prescribed for at least 3 months, the mean follow-up limited to 18 months and the incidence of CVA not mentioned.

Consequently, we would like the investigators to share their long-term results on freedom from thromboembolism associated with the innovative approach proposed. A minimally invasive method for removing and/or occluding the LAA would provide a valuable strategy for preventing stroke in patients with AF. Both percutaneous LAA occlusion and thoracoscopic LAA amputation have been recently developed, although further studies are needed to confirm the safety and efficacy of these approaches (7,9). Additional investigation is needed to determine whether LAA obliteration, which might have a potential clinical impact similar to carotid endarterectomy, is effective in preventing thromboembolism and whether it can be advocated as a "must" in the treatment of a selected population of patients with AF.

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REPLY

We would like to thank Dr. Bonanomi and colleagues for their interest in our work and for their thorough comments. The spectrum of patients with atrial fibrillation (AF) is very wide and varies from the 35-year-old manager with recurrent weekly paroxysms of AF resistant to antiarrhythmic drugs and severe symptoms to the 75-year-old man with hypertension and concomitant asymptomatic rate-controlled AF. Effective and safe treatment strategies are available for many patients, and these often consist of