Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 44, No. 6, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2004.06.026

EDITORIAL COMMENT

Interleukin-10: Biomarker or Pathologic Cytokine in Fulminant Myocarditis?*

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". . . science, I am told, may go astray: the doctors [are] not able to discriminate between the counterfeit and the real."
Fyodor Dostoevsky, *The Brothers Karamozov*, 1879

Sensitive and specific serologic markers for myocardial infarction (MI) and heart failure (HF) are now being incorporated into routine clinical practice with a great influence on physicians' decision making. To have such serologic markers for myocarditis is a worthy goal because the diagnosis depends on a non-specific clinical history and findings, exclusion of other cardiovascular diseases, and/or endomyocardial biopsy, a highly invasive procedure that has poor sensitivity (1–3). Indeed, discrimination between patients with a favorable prognosis and those without is currently more in the realm of art than science.

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In this issue of the *Journal*, Nishii et al. (4) addressed a challenging question: "are there serologic biomarkers that will predict the prognosis of patients with fulminant myocarditis?" This is a particularly important question because it has been demonstrated that despite the severity of disease at presentation, a high percentage of patients will survive and completely recover once they overcome the acute phase (5). Given the effectiveness of cardiac assist devices in patients falling into the category of severe HF who are being treated with high doses of catecholamines, it would be valuable to have serologic markers that would identify those patients who are most likely to need mechanical support and those who are not. To address these questions, the authors studied 22 consecutive patients that fit the definition of fulminant myocarditis: a distinct onset of HF after flu-like symptoms requiring high-dose catecholamines with histologically proven myocarditis (5,6). The patients were then classified into three groups: group 1—patients who had already lapsed into cardiogenic shock requiring mechanical cardiopulmonary support on admission; group 2—patients who unexpectedly lapsed into cardiogenic shock requiring mechanical cardiopulmonary support more than two days after high-dose catecholamine treatment had started; and group 3—patients who required only high-dose catecholamines without mechanical cardiopulmonary support.

Of the alterations that were observed in serum cytokines and C-reactive protein (CRP), the most striking finding was that the admission serum interleukin (IL)-10 level discriminated patients who would require mechanical cardiopulmonary assistance after admission to be discriminated from those who would not require such assistance. In addition, those who would ultimately die from their disease had the highest levels of IL-10. Importantly, average serum IL-10 levels were higher in patients with fulminant myocarditis than in patients with acute MI who also required mechanical cardiopulmonary support, and none of the patients with either fatal or non-fatal MI requiring mechanical support had IL-10 levels as high as those that died of fulminant myocarditis. These findings indicate that IL-10 might be a useful prognostic marker in patients with fulminant myocarditis, whereas other inflammatory markers such as tumor necrosis factor alpha and serum CRP were not as predictive for mortality and the need for mechanical support in this study. In addition, these data demonstrate that inflammatory markers such as IL-10, tumor necrosis factor alpha, and CRP are higher in patients with fulminant myocarditis than in severely ill patients with acute MI. Although this is not particularly surprising, given the inflammatory nature of myocarditis, it sheds a ray of hope that there may be a profile of serologic biomarkers that will discriminate myocarditic from non-inflammatory causes of cardiac dysfunction. Their findings provide meaningful prognostic and diagnostic information that could be useful in the management of patients with fulminant myocarditis.

PROGNOSIS OF FULMINANT VERSUS ACUTE NON-FULMINANT MYOCARDITIS

If we focus on acute myocarditis only, a somewhat paradoxical observation has been reported: patients with fulminant myocarditis have an excellent long-term prognosis despite very severe hemodynamic compromise upon presentation. A clinicopathologic classification using both histologic and clinical features has been published that provides prognostic information in patients with acute myocarditis (6). Based on this classification, a prospective study was performed that demonstrated that 93% of patients with fulminant myocarditis were alive without heart transplantation 11 years after diagnosis, compared with only 45% of those with acute non-fulminant myocarditis (5). These observations strongly support aggressive therapy, including mechanical cardiac

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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support, when necessary, in patients with fulminant myocarditis (7–10).

POTENTIAL IMPACT OF SERUM IL-10 LEVELS ON CLINICAL MANAGEMENT

The cause of myocarditis in a given patient has been very difficult to define; however, pertaining to fulminant myocarditis, the article by Nishii et al. (4) suggests that IL-10 levels could facilitate the management of patients with fulminant myocarditis by predicting those that are likely to develop severe hemodynamic compromise requiring a ventricular assist device. Although the data do not address whether early implantation of a cardiac assist device would be beneficial in patients with high levels of IL-10, they do suggest that more intense monitoring and management could be appropriate in these patients. For example, in the setting of high IL-10 levels, surgeons could be notified of the patient's status, and preparations for potential implantation of a ventricular assist device could be undertaken. Alternatively, in the setting of lower IL-10 levels, a less aggressive management strategy may be appropriate.

A PATHOGENIC ROLE FOR IL-10 IN MYOCARDITIS?

The data presented in the study by Nishii et al. (4) demonstrate that IL-10 might be used as a prognostic biomarker in myocarditis; however, the strong association between IL-10 and prognosis raises the question of whether IL-10 levels may have a pathogenic role in the course of myocarditis as well. It is known that both direct viral injury and the immune response of the host can have important roles in myocarditis (11). Results from experiments in murine models of myocarditis indicate that although the immune response has an important protective role, it also may have deleterious effects on the host. The balance between these protective and deleterious effects may ultimately determine the course of disease after enteroviral infection.

Interleukin-10 generally is thought of as an immunosuppressive cytokine (12), but its exact role in myocarditis is not clear. It has been demonstrated that IL-10 has a protective role in experimental autoimmune myocarditis (13). Alternatively, it is conceivable that induction of an IL-10 immunosuppressive effect could decrease the host defense against viral infection and thus be detrimental to the host. An example of where this appears to be true is in relation to the Epstein-Barr virus, which has incorporated a copy of IL-10 known as viral interleukin (vIL)-10 into its genome (14). Because Epstein-Barr has evolved with vIL-10 in the genome, it is likely that it is beneficial to viral replication.

Although the data presented by Nishii et al. (4) do not define a pathologic role for IL-10 in myocarditis, the data do suggest the testable hypothesis that high levels of IL-10 could have a role in the pathogenesis of the disease: a mechanism that could have implications on its diagnosis and treatment.

FUTURE DIRECTIONS

On the basis of this initial result, consideration should be given to a multi-center study employing a larger population to confirm the significance of serum IL-10 levels in patients with both fulminant and non-fulminant myocarditis, including chronic active or persistent myocarditis. Given the difficulty of diagnosis of myocarditis, it would be valuable if a "footprint" of myocarditis could be defined using serum markers in place of myocardial biopsy. Ideally, this should include prognostic and etiologic markers of the disease. Although these goals may seem to be out of reach, it was not long ago that the best biomarker for MI was measurement of lactate dehydrogenase and serum glutamic oxaloacetic transaminase, enzymes that are expressed at high levels in the liver. Now, serum levels of highly specific and sensitive markers of MI are available that provide valuable prognostic information. We can only anticipate that consistent steady progression of knowledge from bench to bedside will facilitate diagnostic and prognostic breakthroughs in this seemingly invincible disease, thus providing a scientific tool that will discriminate between real myocarditis and its counterfeits.

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REFERENCES

1. Mason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. N Engl J Med 1995;333:269–75.
2. Chow LH, Radio SJ, Sears TD, McManus BM. Insensitivity of right ventricular endomyocardial biopsy in the diagnosis of myocarditis. J Am Coll Cardiol 1989;14:915–20.
3. Hauck AJ, Kearney DL, Edwards WD. Evaluation of postmortem endomyocardial biopsy specimens from 38 patients with lymphocytic myocarditis: implications for role of sampling error. Mayo Clin Proc 1989;64:1235–45.
4. Nishii M, Inomata T, Takehana H, et al. Serum levels of interleukin-10 on admission as a prognostic predictor of human fulminant myocarditis. J Am Coll Cardiol 2004;44:1292–7.
5. McCarthy RE, 3rd, Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. N Engl J Med 2000;342:690–5.
6. Lieberman EB, Hutchins GM, Herskowitz A, Rose NR, Baughman KL. Clinicopathologic description of myocarditis. J Am Coll Cardiol 1991;18:1617–26.
7. Rockman HA, Adamson RM, Dembitsky WP, Bonar JW, Jaski BE. Acute fulminant myocarditis: long-term follow-up after circulatory support with left ventricular assist device. Am Heart J 1991;121:922–6.
8. Chang AC, Hanley FL, Weindling SN, Wernovsky G, Wessel DL. Left heart support with a ventricular assist device in an infant with acute myocarditis. Crit Care Med 1992;20:712–5.
9. Jett GK, Miller A, Savino D, Gonwa T. Reversal of acute fulminant

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September 15, 2004:1298–300

lymphocytic myocarditis with combined technology of OKT3 monoclonal antibody and mechanical circulatory support. J Heart Lung Transplant 1992;11:733–8.
10. Yasu T, Murata S, Katsuki T, et al. Acutely severe myocarditis successfully treated by percutaneous cardiopulmonary support applied by a newly developed heparin-binding oxygenator and circuits. Jpn Circ J 1997;61:1037–42.
11. Knowlton KU, Badorff C. The immune system in viral myocarditis: maintaining the balance. Circ Res 1999;85:559–61.
12. Mocellin S, Marincola F, Rossi CR, Nitti D, Lise M. The multifaceted relationship between IL-10 and adaptive immunity: putting together the pieces of a puzzle. Cytokine Growth Factor Rev 2004; 15:61–76.
13. Watanabe K, Nakazawa M, Fuse K, et al. Protection against autoimmune myocarditis by gene transfer of interleukin-10 by electroporation. Circulation 2001;104:1098–100.
14. Salek-Ardakani S, Arrand JR, Mackett M. Epstein-Barr virus encoded interleukin-10 inhibits HLA-class I, ICAM-1, and B7 expression on human monocytes: implications for immune evasion by EBV. Virology 2002;304:342–51.