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Interferon-Beta Improves Survival in Enterovirus-Associated Cardiomyopathy

To the Editor: Enteroviral myocarditis is a life-threatening disease and a frequent cause of terminal heart failure and increased mortality independently from the severity of left ventricular dysfunction, affecting small children and adolescents even more frequently than adults (1,2). The course varies from subclinical to fulminant disease and may insidiously progress to dilated cardiomyopathy. We previously demonstrated that a 6-month treatment course with interferon-beta (IFN-β) effectively cleared the virus from the hearts of all treated patients with chronic enteroviral cardiomyopathy and improved medical conditions significantly (3). In the short run, spontaneous and treatment-induced virus clearance was associated with clinical and hemodynamic improvement, while patients with persisting infection slowly deteriorated (3,4). To gain insight into the long-term effects of IFN-β treatment, we followed up the patients from first diagnostic biopsy to as long as 120 months and compared their outcome with treated and untreated enterovirus infections.

Only patients with both biopsy-based baseline and follow-up information on the course of the virus infection analyzed by nPCR were included in this investigation. We identified 96 patients with symptoms of heart failure (for >6 months) including fatigue and reduced physical capacity (69%), dyspnea on exertion (71%), angina at rest (36%), or palpitations (38%) and arrhythmias (40%). Most patients were in New York Heart Association functional classes II and III (class II, 54%; class III, 28%; and class IV, 4%). Histological and immunohistological evaluation revealed no significant baseline differences between patients with spontaneously cleared and not cleared viral infection (CD3-positive lymphocytes: 7 ± 10 cells/mm^2 vs. 6 ± 10 cells/mm^2, respectively; p = 0.61). The diagnostic procedures have been described earlier (4,5).

The short-term clinical course of 14 consecutive patients treated with IFN-β in a first pilot study, 28 patients with spontaneous enterovirus clearance, and 28 patients with biopsy-proven virus persistence have already been reported (3,4). Fourteen of the 28 patients with persisting viral infection could be treated with IFN-β, because the treatment costs were covered by their health insurances. The other 14 patients, 7 patients with newly diagnosed persisting, and 19 patients with spontaneously cleared infections completed the study group of 96 patients.

The interval between baseline and follow-up biopsy was 9.5 ± 7.6 months for patients who cleared the viral infection (n = 47; 29 male; mean age 47 ± 15 years) and 11.0 ± 7.4 months for patients with viral persistence (n = 49; 33 male; mean age 51 ± 12 years; p = 0.123). All patients received heart failure medication including angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers (67%), beta-blockers (65%), spironolactone (45%), and diuretics (55%), without significant differences among the 3 analyzed cohorts. An implantable cardioverter-defibrillator or pacemaker was received by 2/0 of IFN-treated patients, 4/1
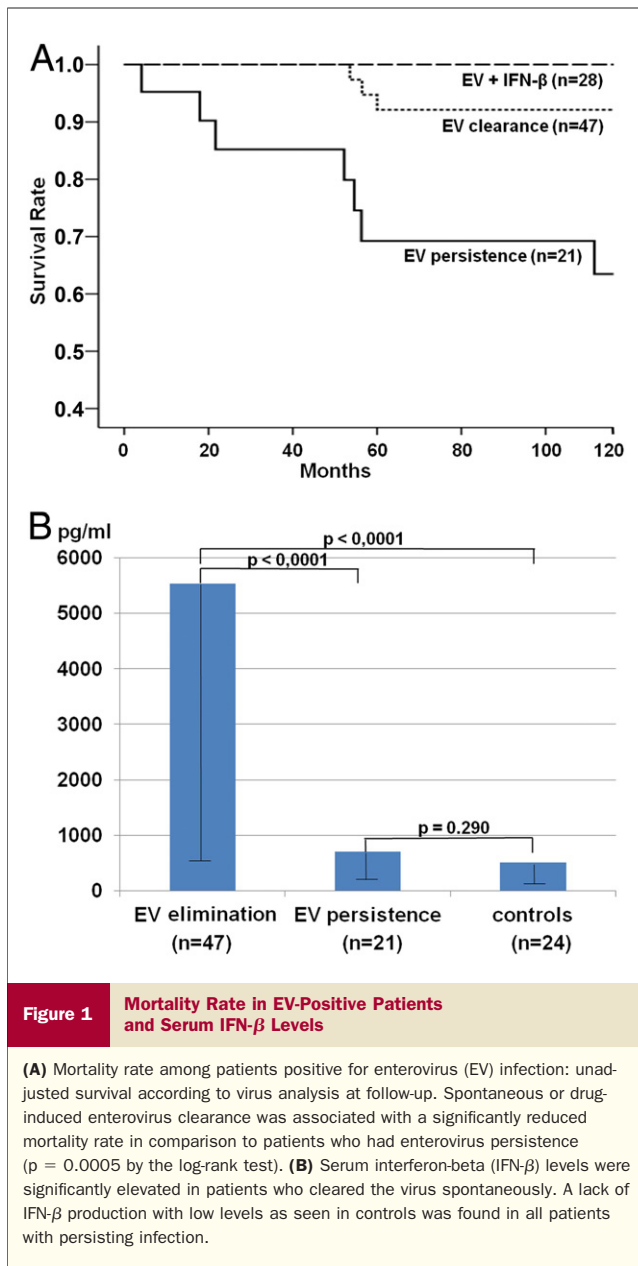
patients with cleared virus, and 3/2 patients with virus persistence, respectively.

In the interferon treatment group (n = 28; 16 male; mean age 48 ± 1 years), the treatment started within 4 months after the virus-positive follow-up biopsy. Eight million units of IFN-β were administered every other day for 6 months in addition to constant heart failure medication. The treatment procedure has been reported earlier (3). Treated patients underwent follow-up biopsy 8.3 ± 2.2 months after the start of the 6 months' IFN-β treatment course.

For the IFN-β serum level analysis, venous plasma samples were obtained by standard venipuncture immediately before the biopsy procedure and immediately frozen at −80°C. All samples were analyzed simultaneously in duplicates by commercially available single-plate enzyme-linked immunosorbent assay kits.

All patients lived in the catchment area of our hospital, enabling us to obtain long-term information on patients' outcome. Occurrence of the endpoint death was determined through direct contact with the patient, contact with family members, inquiries at the registration office, or all 3. Qualitative data were compared by conducting the chi-square test. Student's t test was used to analyze continuous variables. A probability value of a 2-sided p < 0.05 was considered statistically significant. Survival curves were generated according to the Kaplan-Meier method and were compared with the log-rank statistic. Patients who did not meet the 10-year endpoint became censored at the point of their last follow-up. All analyses were performed using JMP Statistical Discovery Software 7.0 (SAS Institute, Cary, North Carolina).

Patients with persisting virus infection had significantly lower left ventricular ejection fraction (EF) than patients who cleared the virus from their myocardium (p < 0.003). Patients with spontaneous enterovirus elimination confirmed by follow-up biopsy were significantly less likely to die during a mean follow-up of 91 ± 37 months than were patients with virus persistence (mean follow-up 84.4 ± 45 months). Upon IFN-β treatment, all 28 patients cleared the enteroviral infection from the myocardium. In the long-term survival analysis (mean follow-up 95.8 ± 36 months), outcome of treated patients was considerably improved. As shown in Figure 1A, the mortality rate was low among patients who spontaneously cleared their cardiac viral infection, whereas 52.5% of patients with biopsy-proven enterovirus persistence met the endpoint of death. At 5 years, 92% of patients who had cleared the virus (n = 45 [EF$_{baseline}$ 53 ± 16%, EF$_{follow-up}$ 58 ± 1%], p = 0.001) were alive, in contrast to only 69% of patients with virus persistence (n = 12 [EF$_{baseline}$ 39 ± 18%, EF$_{follow-up}$ 41 ± 16%], p = 0.37). Remarkably, all IFN-β-treated patients (n = 28 [EF$_{baseline}$ 52 ± 17%, EF$_{follow-up}$ 58 ± 14%], p = 0.04) were alive at the end of study. Patients with EF <45% (n = 10) as well as patients with EF >45% (n = 18) achieved long-term benefits from IFN-β treatment.

Figure 1 **Mortality Rate in EV-Positive Patients and Serum IFN-β Levels**

(A) Mortality rate among patients positive for enterovirus (EV) infection: unadjusted survival according to virus analysis at follow-up. Spontaneous or drug-induced enterovirus clearance was associated with a significantly reduced mortality rate in comparison to patients who had enterovirus persistence (p = 0.0005 by the log-rank test). (B) Serum interferon-beta (IFN-β) levels were significantly elevated in patients who cleared the virus spontaneously. A lack of IFN-β production with low levels as seen in controls was found in all patients with persisting infection.

Because IFN-β cleared the enterovirus infection effectively, we compared the serum IFN-β levels with the course of the virus infection in untreated patients. Serum IFN-β levels were significantly elevated in patients who cleared the virus spontaneously (n = 47), both in comparison with healthy controls (n = 24) and with patients having virus persistence (n = 28) (Fig. 1B).

Enterovirus persistence is associated with a significantly higher risk of death for those patients compared with patients capable of inducing spontaneous virus elimination. Both spontaneous IFN-β production in response to infection and IFN-β administered over 6 months were associated with effective enterovirus clearance and improved outcome. The lack of spontaneous IFN-β production was associated with enterovirus persistence. The precise mechanism by which enterovirus infection affects prognosis, whether by altering myocardial function or by inducing arrhythmias, remains a matter for speculation (5). Our data suggest that administration of IFN-β may favor virus clearance and reduce progression of virus-induced myocardial injury, with improved long-term survival as seen in patients with spontaneous virus clearance. This finding suggests that antiviral treatment should be started in time before irreversible myocardial damage has developed.

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