Long-term follow up of patients with dilated heart muscle disease treated with human leucocytic interferon alpha or thymic hormones

Initial results

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Abstract

Objective—To determine whether giving interferon- α or thymomodulin in addition to conventional treatment improves cardiac function in patients with idiopathic myocarditis and idiopathic dilated cardiomyopathy.

Design—Single-centre, randomised, open label, parallel group comparison of conventional treatment plus interferon- α , conventional treatment plus thymomodulin, and conventional treatment alone.

Patients—38 patients aged 19–54 years (23 men) with biopsy-proven myocarditis or dilated cardiomyopathy. 12 were treated with conventional treatment alone, 13 were treated with interferon- α and conventional treatment, and 13 with thymomodulin and conventional treatment.

Setting—Tertiary cardiac referral centre.

Main outcome measures—Clinical evaluation, echocardiography, and Holter monitoring at baseline, 6 months, and 1 and 2 years. Radionuclide ventriculography at rest and during exercise after 2 years. Endomyocardial biopsy at baseline and after a year if the initial diagnosis was myocarditis.

Results—Left ventricular ejection fraction was improved in 21 (81%) of 26 patients after interferon- α or thymomodulin administration and in 8 (66%) of 12 conventionally treated patients ($P < 0.05$) at 2 year follow up. The maximum exercise time was significantly longer at 2-year follow up in patients treated with immunomodulators (mean (SEM) 5.1 (0.6) minutes for interferon- α and 5.0 (0.4) minutes for thymomodulin) than in conventionally treated patients (3.3 (0.4) minutes). Left ventricular ejection fraction during exercise (assessed by radionuclide ventriculography) improved in 9 of 12 patients treated with interferon- α , 10 of 12 patients treated with thymomodulin, and 3 of 9 conventionally treated patients at 2 year follow up. The electrocardiogram was normal in 21 (88%) of 24 patients after interferon- α or thymomodulin treatment and 2 (22%) of 9 conventionally treated patients. At 2 year follow up, 19 (73%) of 26 patients treated with immunomodulators and 4 (25%) of 12 conventionally treated patients had improved their functional class.

Conclusions—The results suggest that

treatment of idiopathic myocarditis and/or idiopathic dilated cardiomyopathy with interferon- α or thymomodulin induces an earlier and significantly superior clinical improvement than conventional treatment alone.

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Keywords: idiopathic myocarditis; idiopathic dilated cardiomyopathy; interferon- α ; thymic hormones

Enteroviruses and other viruses or viral sequences have been found in the cardiac tissues of patients with idiopathic myocarditis and idiopathic dilated cardiomyopathy.^{1–3} Possibly cardiotropic viruses cause not only a symptomatic or asymptomatic initial infection but also persist in the myocardium of some patients.^{4–6} During persistent infections there is frequently a reduction in the virally encoded surface glycoproteins expressed on the outer membrane of infected cells.^{7,8} This reduction in viral proteins on infected cells provides an advantage for the persisting virus, because such cells are less vulnerable to immunological attack by humoral or cell-mediated effector mechanisms. At the same time, such infected cells fail to activate lymphocytes with natural killer cell activity.⁹ A deficiency in host defenses, such as the interferon system, might contribute to the development of persistent infections. If viruses do cause idiopathic myocarditis and some cases of idiopathic dilated cardiomyopathy, treatment with interferon or its inducers may be appropriate, either because of its direct action on the target cell or indirect effects (activation of cytotoxicity, modulation of immune responses, and interaction with other mediators of immune response). This was the rationale for our clinical trial of interferon- α or thymic hormones in patients with dilated heart muscle disease. We chose interferon- α because it is highly diffusible and easily reaches distant organs after subcutaneous injection and thymic hormones because they induce a rise in the concentration of endogenous interferon and stimulate natural killer and T cell activities.¹⁰ We performed a serial evaluation of clinical data over a two year period to document the possible influence of immunomodulatory treatment on the natural course of idiopathic myocarditis and idiopathic dilated cardiomyopathy, because these diagnoses could represent two forms of the same disease.¹¹

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Patients and methods

We studied 38 patients (15 women and 23 men) in whom the diagnosis of idiopathic myocarditis or idiopathic dilated cardiomyopathy had been confirmed by biopsy and who had a left ventricular ejection fraction (LVEF) of < 45% at angiography. Those with postpartum and familial cardiomyopathy, giant-cell myocarditis, and all forms of secondary myocarditis were excluded, as were patients with ischaemia, valvar or congenital heart disease, severe hypertension, alcoholism, pregnancy or postpartum, and autoimmune or other life-threatening disease. Initial evaluation included clinical symptoms, immunological tests, chest x rays, electrocardiogram, cross sectional echocardiographic examination, right and left heart haemodynamic studies, and right ventricular endomyocardial biopsy. Three or four myocardial tissue samples were taken and studied by light microscopy to establish the histological diagnosis, according to the Dallas criteria¹² (femoral approach, King's biptome). Molecular biological techniques including in situ hybridisation and polymerase chain amplification were not available at the time of the study.

IMMUNOLOGICAL INVESTIGATIONS

Blood was taken for measurement of virus neutralising antibody titres, humoral, and cellular studies. Humoral studies included: (a) a search for circulating antibodies against cardiac muscle, skeletal muscle, smooth muscle, and parietal cells as well as those against components of the nuclei and the mitochondria (immunofluorescence assay)¹³; (b) analysis of sera for IgM, IgG, IgA, IgD, and IgE, (laser nephelometry)¹⁴; and (c) detection of circulating immune complexes (laser nephelometry with LN Latex CIC Reagent, Behring).¹⁵ Among cellular studies, phenotyping of peripheral blood mononuclear cells and natural killer cell assay (⁵¹Cr release assay)¹⁶ were performed to define the patient's lymphocyte subpopulations and non-specific cell-killing ability. For phenotyping of peripheral blood mononuclear cells we used monoclonal antibodies (OKT3, OKT4, OKT8 (Ortho Diagnostics, Raritan, NJ) and Leu-7 (Becton-Dickinson, Mountain View, CA)), fluorescein isothiocyanate staining, and flow cytometric enumeration.¹⁷⁻¹⁹ Immunological studies were repeated weekly and monthly during the first six months of follow up.

The study design was a prospective, randomised, open label comparison of conventional treatment with conventional treatment plus immunomodulation with interferon- α or thymic hormones. After approval by the Institution Review Board and after consent forms were signed, the patients were randomly assigned to three treatment groups: (1) 12 patients received conventional treatment for congestive heart failure, (2) 13 patients received conventional treatment plus interferon- α ; and (3) 13 patients received conventional treatment plus thymic hormone. Treatment lasted for three months. For the next three months all patients received con-

ventional treatment alone. The criteria for administration of conventional treatment were set at the beginning of the study. A specific stepwise conventional regimen, with identical doses in all treatment groups, was given by the same physician in the order listed below:

- reduced salt intake (less than 4 g a day).
- Digoxin (serum concentration of 1–2 mg/ml).
- Frusemide (40–160 mg/day).
- Captopril (25 mg three times a day).
- Metolazone (2.5–5 mg/day).
- Warfarin (if LVEF was < 35%) to maintain the international normalised ratio for prothrombin time in the range 2.5–4.0.

These steps were followed in order as necessary.

Purified leucocytic interferon- α (Torlak, Beograd) was given at 3 million U/m² of body surface area subcutaneously three times a week. Thymus-TFX Thymomodulin (10 mg) (Thymoorgan, Pharmazie, Vieneburg, Germany) was given subcutaneously three times a week. Thymus-TFX thymomodulin is a biologically active extract of the thymus gland of calves consisting of polypeptides between 4000 and 6000 daltons.

At six month, one year, and two year follow up we performed clinical evaluation, echocardiographic studies (biplane method for LVEF measurements), chest x rays, and Holter monitoring. At one year, we repeated the right ventricular endomyocardial biopsy if the initial diagnosis was myocarditis. At two years radionuclide ventriculography gated blood-pool technique was performed at rest and during exercise.

STATISTICAL ANALYSIS

Measurements were mean (SEM). Statistical analysis was performed using analysis of variance for repeated measures (Newman-Keuls multiple comparisons) and analysis of variance by the modified *t* test (Bonferroni) as appropriate. Results were regarded as significant if *P* was less than 0.05.

Results

Four patients had histological diagnosis of active and 11 patients of borderline myocarditis. Their average age at presentation was 29.3 years (range 19–40 years). Twenty three patients had a histological diagnosis of idiopathic dilated cardiomyopathy (mean age at presentation of 31.7 years (range 19–54 years)).

We found raised virus neutralising antibody titres, usually to Coxsackie B viruses, in 14 patients.

At the start of the study two patients were in New York Heart Association class II, 26 patients were in class III, and 10 in class IV. There was no significant baseline medical difference among the three treatment groups. Left ventricular function assessed by angiography at the beginning of the study was similar (LVEF was 22.7 (1.2)% in patients treated with interferon- α , 22 (14)% in patients treated with thymomodulin, and 23.9 (1.1)% in con-

Figure 1 Natural killer cells as a percentage of peripheral blood mononuclear cells (PBMC) in 38 patients with dilated heart muscle disease during treatment. IFN, interferon- α ; TH, thymomodulin, $P < 0.0001$ (ANOVA for repeated measures, Newman-Keuls multiple comparisons, error bars = SEM).

Figure 2 Effects of three treatments on natural killer cell activity and neutralising antibody titres during six month follow up in 38 patients with dilated heart muscle disease. IFN = Interferon- α .

Figure 3 Effects of three treatments on left ventricular ejection fraction (LVEF) in 38 patients with dilated heart muscle disease treated with IFN- α and conventional treatment; thymomodulin and conventional treatment, and conventional therapy alone (mean (SEM), $P < 0.0001$) (ANOVA for repeated measures, Newman-Keuls multiple comparisons).

Left ventricular ejection fraction (LVEF) at the beginning of the study and after two year follow up in patients with dilated heart muscle disease according to diagnosis and treatment

No	Start	No	2 y
Idiopathic myocarditis:			
5	23.0 (1.2)	31.0 (2.1)	
5	23.6 (1.3)	32.8 (1.4)	
5	23.4 (1.0)	27.6 (1.4)	
IDC:			
8	22.5 (1.1)	7	29.4 (2.3)
8	21.0 (1.5)	7	29.1 (1.6)
7	24.1 (1.2)	4	26.2 (1.7)

ventionally treated patients). Thirty five patients had electrocardiographic abnormalities. Natural killer cells were absent or significantly decreased in all patients, while natural killer cell activity was low in 35 patients.

The relative number of natural killer cells increased significantly after two weeks of treatment in the interferon- α group and returned to the baseline count after six months (fig 1). In contrast to this sharp, short term increase in natural killer cells, we found a progressive, long term increase in the thymomodulin group. A significant increase in natural killer cell activity was seen in the interferon- α and thymomodulin treated patients. This started at two weeks and lasted for months (from 30.6 (1.4)% to 48.5 (1.9)% in the interferon- α group, and from 28.6 (1.2)% to 44.7 (1.6)% in the thymomodulin group). We did not find a change in natural killer cell activity in conventionally treated patients ($P < 0.0001$, analysis of variance for multiple comparisons). Increase in the relative number of natural killer cells and natural killer cell activity was followed by significant decrease in neutralising antibody viral titres in patients treated with immunomodulators (fig 2).

In 10 interferon- α treated and 11 thymomodulin treated patients, resting LVEF assessed by echocardiography improved at six months and showed further improvement at two year follow up (fig 3). Resting LVEF improved in eight conventionally treated patients at two year follow up. This improvement was found in a significantly lower proportion than in patients treated with immunomodulators ($P < 0.05$, analysis of

Figure 4 Left ventricular ejection fraction (LVEF) during exercise in 33 patients at two year follow up during treatment with IFN- α and conventional treatment, thymomodulin and conventional treatment, and conventional treatment alone (mean (SEM), $P < 0.0001$) (ANOVA for repeated measures, Newman-Keuls multiple comparisons).

variance for multiple comparisons). The table shows changes in resting LVEF during two year follow up in the treatment groups according to the diagnosis. There were too few patients in each group for these changes to be analysed statistically. At the two year follow up left ventricular ejection fraction was higher at peak exercise than at rest in nine patients treated with interferon- α and 10 with thymomodulin (fig 4). In seven conventionally treated patients, the ejection fraction decreased or failed to increase on exercise, indicating an abnormal haemodynamic response. Maximum exercise time at two year follow up was 5.1 (0.6) minutes in the interferon- α group, 5 (0.4) minutes in thymomodulin group, and 3.3 (0.4) minutes in the conventionally treated group ($P < 0.01$, analysis of variance, modified t test, Bonferroni).

Biopsy was repeated at one year. In five patients with initial diagnosis of myocarditis who were treated with interferon- α (two active and three borderline) myocarditis had resolved. Of five patients treated with thymomodulin (one active and four borderline myocarditis), one had resolving myocarditis and four had resolved myocarditis. In the conventionally treated group, one patient who initially had active myocarditis had resolving myocarditis, two who initially had borderline myocarditis had resolved myocarditis, and two who initially had borderline myocarditis had a histological diagnosis of dilated cardiomyopathy.

In nine patients treated with interferon- α and six treated with thymomodulin NYHA class had improved at one year (fig 5). At two year follow these patients maintained their improvement. In five conventionally treated patients the functional class had improved at one year, and in one of them it had worsened again at two year follow up.

One interferon- α treated patient with biopsy confirmed idiopathic dilated cardiomyopathy died five months after presentation. It was a sudden death outside hospital. One thymomodulin treated patient died at nine months of an embolic cerebrovascular accident. Three patients in the conventionally treated group died during two year follow up—one suddenly and two from end stage cardiac failure.

Discussion

Dilated heart muscle disease can be idiopathic (IDC) or secondary to other causes, such as viral myocarditis or viral perimyocarditis.²⁰ The criteria for IDC in our study were angiographic evidence of cardiomegaly and reduced ejection fraction ($< 45\%$); exclusion of coronary artery disease, valvar heart disease, hypertension, and other forms of secondary heart muscle diseases; and histopathological findings of hypertrophy and branching of the myocytes, with diffuse or focal fibrosis. The criteria for idiopathic myocarditis were biopsy confirmed inflammation of the myocardium with infiltrate, focal necrosis, and interstitial oedema with or without fibrosis. Fourteen patients also had significant changes ($> three$ -fold increase) in virus neutralising antibody titres against cardiotropic viruses. RNA and DNA probes for cardiotropic viruses were not available in our study.

Though there are many causes of dilated cardiomyopathy and the aetiology is frequently difficult to determine, it is becoming increasingly apparent that after an acute or subacute episode of viral myocarditis the virus can persist in the cardiac tissues and cause dilated cardiomyopathy.^{6,21} In human diseases thought to be caused by putative persistent infections,

Figure 5 NYHA classification at two year follow up in 38 patients with dilated heart muscle disease.

there is evidence of diminished interferon production and natural killer activity by lymphocytes.^{22,23}

Left ventricular ejection fractions improved in 21 (81%) of 26 patients after interferon- α or thymomodulin administration and to a lesser extent in eight (66%) of 12 conventionally treated patients ($P < 0.01$) at six month follow up. Maximum exercise time was significantly longer at two year follow up in patients treated with immunomodulators. Left ventricular reserve, assessed by rest and exercise radionuclide ventriculography was significantly higher in patients treated with interferon- α or thymomodulin. The electrocardiogram was normal in 21 (88%) of 24 patients after interferon- α or thymomodulin treatment and in two (22%) of nine conventionally treated patients. At two year follow up, 19 (73%) of 26 patients treated with immunomodulators and four (25%) of 12 conventionally treated patients showed an improvement in functional class.

We found a significant increase in relative number of natural killer cells and enhancement of natural killer cell activity in patients treated with interferon- α or thymomodulin. Both the increase in natural killer cell number and activation occurred quickly with interferon- α and disappeared after four weeks of treatment. Activation was slower with thymomodulin but lasted significantly longer. Patients treated conventionally had no changes in relative number of natural killer cells and natural killer cell activity.

Increased natural killer cell activity is associated with a more effective inflammatory response and less severe initial myocarditis.²⁴ The natural killer cell response is mainly responsible for elimination of virus in the early phase of the disease, but when viral infection persists it could also be important in eliminating virus in late phase of the disease. Our findings accord with the suggestion of Mason *et al.*²⁴ that a strong spontaneous immune response could be a beneficial rather than an initiating factor in myocarditis²⁴ and also with the concept that stimulation of the immune response by immunomodulators could be of benefit even in idiopathic dilated cardiomyopathy.

Our data strongly suggest treatment of myocarditis and idiopathic dilated cardiomyopathy with interferon- α or thymomodulin, and in our opinion they accord with the conclusions of Mason *et al.*, who do not recommend the routine use of immunosuppressive drugs. Nonetheless, immunohistological findings in some groups of patients indicate that immunosuppressive drugs may be beneficial.

There were minor complications of endomyocardial biopsy in two of the 38 patients before treatment was started and in one (6%) of the 15 repeat biopsies. Eleven of the 13 patients treated with interferon- α had a 'flu-like symptom dominated by fever, a few hours after the start of treatment. The peak temperature tended to decrease with repeated injections and usually disappeared after 10 days of treatment. In two patients it was associated

with lassitude and malaise. Cardiovascular and neurological symptoms were not reported. Reversible mild leucothrombocytopenia was seen in six patients. Treatment did not have any significant effect on serum transaminases. Reversible heart dilatation²⁵⁻²⁷ was not seen either.

Four of the 13 patients treated with thymomodulin had a slight, but transient increase in weight. In two women menstrual bleeding was prolonged.

Patients with a left ventricular ejection fraction $< 30\%$ have a poor prognosis and many such patients are on a progressively downhill course and are likely to die within a few years. The poor prognosis of idiopathic heart muscle disease justifies the continued pursuit of new treatments. We believe that the improvement in cardiac function that occurred during the two year follow up in patients with idiopathic myocarditis or idiopathic dilated cardiomyopathy treated with interferon- α or thymomodulin may have been the result of enhancement of immune function in patients who had a chronic myocardial viral infection.

Our results suggest that a combination of interferon- α and thymomodulin could improve function more than either drug given on its own—because of the early effects of interferon and the sustained effects of thymomodulin on immune function.

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