



# European Society of Cardiology Working Group on Myocardial & Pericardial Diseases

## Newsletter

Issue 14 - July 09



## Editorial News

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Dear Members of the Working Group,

please find enclosed the 14<sup>th</sup> issue of our Newsletter.

In addition to the 'clinical case of the month' and the 'paper of the month' you will find within this issue the case resolution from the June case.

Best wishes for all of you.

*S. Pauhauf*

## The paper of the month:

**Randomized study on the efficacy of immunosuppressive therapy in patients with virus-negative inflammatory cardiomyopathy: the TIMIC study. Andrea Frustaci, Matteo A. Russo and Cristina Chimenti. European Heart Journal published online June 25, 2009**

**Presented by Dr. S. Pankuweit**, University Hospital Marburg, Dept. of Cardiology, Baldinger Str., Marburg, Germany



### Summary:

Currently there is no consensus on the treatment of inflammatory cardiomyopathy with immunosuppression and the strategies used are those adopted for the management of heart failure. The TIMIC study was initiated to evaluate the efficacy of immunosuppression in virus-negative inflammatory cardiomyopathy.

The TIMIC study (1) as a randomized, double-blind, placebo controlled trial included 85 patients with myocarditis and chronic (>6 month) heart failure unresponsive to conventional therapy. All patients have had an endomyocardial biopsy with the presence of > 14 infiltrating leucocytes/mm<sup>2</sup> and/or the presence of more than 2 CD3-positive lymphocytes per high power field (hpf). The presence of the genome of cardiotropic viruses was excluded by polymerase chain reaction with primer pairs specific for the 10 most important cardiotropic viruses (adenovirus, Epstein Barr virus, Human herpes virus 6, Parvovirus B 19, Herpes simplex virus 1-2, Cytomegalovirus, enterovirus, influenza A and B viruses, Hepatitis C virus).

Patients received either prednisone 1mg/kg body weight (BW) per day for 4 weeks followed by 0.33 mg/kg BW for 5 months and azathioprine 2mg/kg BW for 6 month (n=42) or placebo (n=42). All patients were on optimal continuous medication with conventional heart failure therapy including digitalis, diuretics, ACE inhibitors and carvedilol 8 weeks prior and during the study. Primary outcome was the 6 month improvement in left ventricular function, based on the increase of left ventricular ejection fraction assessed by echocardiography. Secondary objectives were changes NYHA functional class and survival differences (cardiac death or heart transplantation).

88% of patients in the treatment group showed a significant improvement of left-ventricular ejection fraction and a significant decrease in left ventricular dimensions and volume compared with baseline. The remaining 5 five patients maintained a stable clinical picture and cardiac function parameters. Even patients with severe advanced disease (LVEDD up to 90mm and LVEF <20%) significantly improved. The percentage of patients who improved by at least 1 NYHA class at 6 month was 49% in the treatment group and none in the placebo group.

None of the patients without specific treatment (placebo) showed improvement of ejection fraction, that significantly worsened compared with baseline in 83% of patients. Seven patients remained stationary. Specifically, after 1 month of treatment, placebo group exhibited in 38% a mild improvement of ejection fraction, that was maintained up to 3 month, but then declined to baseline or lower values.

No major adverse events were registered as a result of immunosuppressive therapy. Minor adverse reactions as increased body weight, glucose blood level elevation, and fluid retention requiring diet, glucoactive drugs, insuline administration, and diuretic dose adjustment were reported in only six patients on immunosuppression.

Control immunohistology at 1 and 6 month showed, that the 38 patients under immunosuppression, who improved, had healed myocarditis with disappearance of inflammatory infiltrates associated with interstitial and focal replacement of fibrosis. In the placebo group findings in endomyocardial biopsies were not dissimilar from baseline, showing persistence of myocarditis as well as expansion of interstitial and replacement fibrosis.

Results of this trial confirmed the positive impact of immunosuppression on recovery of LV function in a high rate of patients with no case of death or cardiac transplantation during treatment and in the following 6 month. Remarkably a striking improvement occurred even in patients with extreme LV dilatation and dysfunction and it was accompanied at histological examination by the disappearance of inflammatory infiltrates with progression of the disease from an active towards a healed myocarditis.

In conclusion, immunosuppressive therapy in patients with *virus-negative* inflammatory cardiomyopathy appears as an effective and safe option in addition to supportive treatment for recovery of cardiac failure.

### Discussion:

There is reasonable clinical and experimental evidence, that DCM may occur as late stage of cardiac infection and inflammation in a subgroup of patients. Heterogeneity of symptoms, with subclinical or asymptomatic forms, could be the reason, why prevalence of myocarditis and the link to DCM may be underestimated. This large spectrum of clinical forms depends on several factors such as genetic determinants of the infective agent, the genetics, age and gender of the host, and the host immunocompetence. With the development of various new diagnostic modalities, early and definite diagnosis of dilated inflammatory or infectious cardiomyopathy depends, first, on the detection of inflammatory infiltrates in the endomyocardial biopsies according the WHO/ISFC and the Dallas criteria using immunohistochemistry. Second, molecular techniques such as polymerase chain reaction (PCR), in situ hybridization, gene sequencing and real-time PCR, often applied on the same endomyocardial specimen, are essential for the rapid, specific and sensitive identification of the infective agents. In addition, the correct application of these methods may allow us to get information on epidemiology, risk stratification in a given patient and a more appropriate medical treatment (2). Because of the overlap of pathophysiological stages in DCM, design of the appropriate therapy is important. It requires the immunohistochemical and molecular biological investigation of endomyocardial biopsies in parallel. Therapy for the first virally or bacterially induced stage needs an effective antiviral or antibacterial treatment, especially as viral infection represents an independent unfavourable prognostic factor in patients. Therapy for the second inflammatory stage is an anti-inflammatory therapy, that on the other hand may be harmful, if virus persists in the myocardium (3).

When planning their study, Frustaci et al. have taken care on the different pathophysiological stages of the disease and have used all of the appropriate diagnostic tools that should be used to differentiate the patients.

For this, the TIMIC trial advances our understanding of the role of inflammation in chronic dilated cardiomyopathy. First, their results provide convincing clinical data showing that persisting inflammation causes myocardial dysfunction in their select population. In addition to this, Kindermann et al. have recently shown, that detection of inflammatory infiltrates in endomyocardial biopsies by immunohistochemistry predict a poor outcome with regard to left ventricular function (4). Persistence of cardiotropic viruses was tested negative by polymerase chain reaction in all of those patients.

Secondly, their use of cell-specific immunocytochemistry to define myocarditis identifies a subset of patients with chronic dilated cardiomyopathy, that respond to immunosuppression. Indirectly, by demonstrating robust improvement in patients without viral genome in the heart, their results support the concept that persistent viral infection is important in the pathogenesis of a different subset of patients with chronic cardiomyopathy (5).

Nevertheless, the clinical endpoints need to be evaluated prospectively because a short-term increase on left ventricular ejection function may not correlate with the long-term risk of death or transplantation in this subset of cardiomyopathy patients.

First answer to this question may arise from the European Study on Epidemiology and Treatment of Cardiac Inflammatory Disease (ESETCID-trial) (6) were patients with autoreactive (virus-negative) myocarditis (AM) and an ejection fraction <45% were randomised for 6 months of treatment with azathioprin (2mg/kg BW/day for 1 month and 0.85mg/kg BW/day for 5 month) + prednisolone (1.25mg/kg BW/ for 1 month and 0.3mg/kg BW/day for 5 month) or placebo on top of their heart failure treatment and followed-up for up to 8 years. 3149 patients with dilated cardiomyopathy were screened, 103 pts (mean age  $47 \pm 9$  years, 81 male, 22 female) with myocarditis and an ejection fraction <45% were randomised for ESETCID after informed consent and continuously follow-up. Endomyocardial biopsies were examined for lymphocytes & macrophages by immunohistochemistry ( $\geq 14$  infiltrating cells/mm<sup>2</sup>), persistence of viral or bacterial genomes for Parvo B19, coxsackie-, influenza-, adeno-, cytomegalo-, HHV 6, EBV, chlamydia and borrelia were excluded from the analysis. 56 patients with myocarditis were treated with verum, 47 patients with placebo. MACE are defined as cardiac death, heart transplantation, ICD implantation or hospitalisation for cardiac decompensation. Time to MACE is given in days to the event. Inflammation was eradicated in 63% in the treatment group, but it also vanished spontaneously in 40% in the placebo arm ( $p < 0,05$  when compared to 100% positive at initiation of therapy). After 12 months the Kaplan Mayer MACE curves began to diverge. At 4 years freedom from MACE was 50% in the verum and 40% in the placebo group. Respective data at 8 years were 40% and 20% freedom from MACE. NYHA-association class and Minnesota Heart Failure Score improved in treatment and placebo arms to a similar extend. Ejection fraction by echo and radioventriculography improved in both arms with a trend for immunosuppression.

Independent from a therapy patients with no inflammation in the follow-up biopsy ( $n=45$ ) showed a better NYHA-class ( $p < 0,05$ ), ejection fraction and superior long term freedom from MACE than those with persistent inflammation.

## Conclusions:


The findings in the Frustaci trial are timely and have potential implications for the worldwide population of patients with dilated cardiomyopathy. The present study also has implications for further therapies such as immunoadsorption or plasmapheresis that may need to demonstrate favourable efficiency and safety against inexpensive and widely available immunosuppressive agents for the treatment of chronic inflammatory cardiomyopathies. Maybe that the Esetcid-trail gives answers with regard to the clinical endpoints death or heart transplantation, as the patient population and treatment is comparable with the TIMIC-trial.

In the modern molecular era the infective agent-immune system-host interaction has become clearer leading to a better knowledge of the etiology of dilated cardiomyopathy. This may change the management of the disease in the future. One of the hopes is to discern the underlying dominant mechanism in a given patient to make a decision for the most promising therapy.

## References

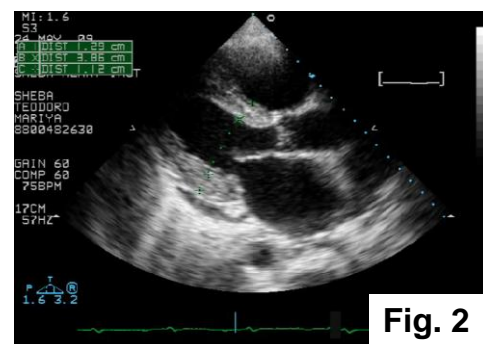
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**Answers will be given in the next newsletter and on the web site**



## Case Presentation:

In May 2009 the patient was in NYHA functional class IV. Her ECG is demonstrated in figure 1. An echo-doppler study showed left ventricular hypertrophy (13mm), LVEF 20%, severe diastolic dysfunction, severe right ventricular dysfunction with dilated inferior vena cava, mild tricuspid regurgitation, normal estimated pulmonary artery pressure and small pericardial effusion (figure 2-5). Cardiac MRI was performed, demonstrating a diffuse late gadolinium enhancement (LGE), more pronounced in the subendocardium (figure 6-7). A diagnostic test was performed.





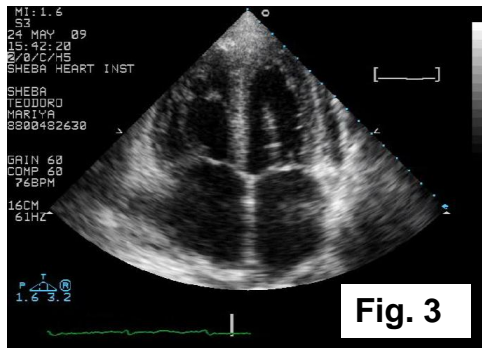


Fig. 3

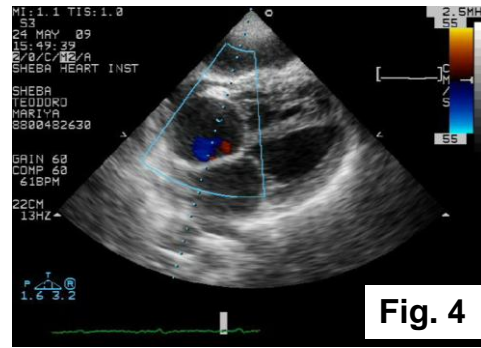


Fig. 4

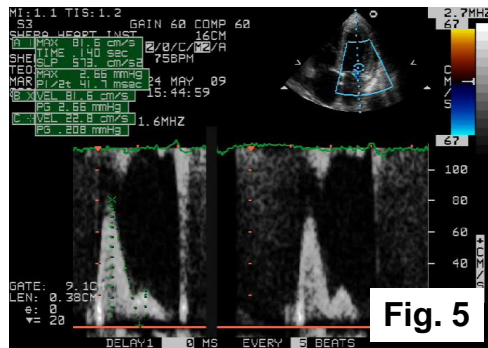


Fig. 5

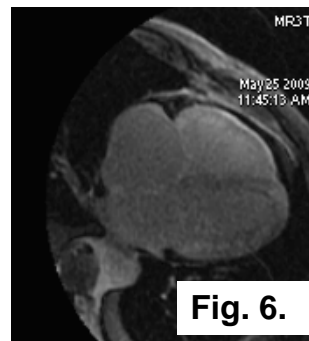


Fig. 6.



Fig. 7

What do you think is the diagnosis in this patient, which further investigations should be performed?

**Answer for the previous “Clinical case of the month” presented in June:**

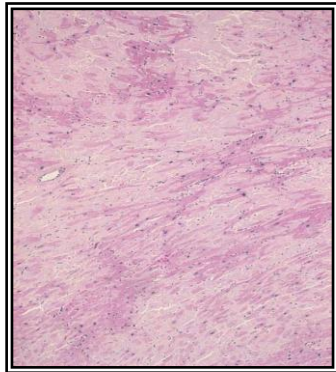
**“A 52 year old male with recurrent abdominal pain”**

**by Dr. Pablo Garcia-Pavia and Dr. P. M. Elliott,** Cardiomyopathy Unit, Heart Transplant Program, Puerta de Hierro University Hospital, Madrid, Spain and Inherited Cardiovascular Disease Unit, Department of Cardiology, The Heart Hospital, University College of London, London, UK.

**Diagnosis, case resolution and treatment**

There were several clues that should have prompted consideration of the diagnosis of cardiac amyloidosis. Specifically: the history of bilateral carpal tunnel surgery; abdominal pain; mild cardiac hypertrophy; and AV block. The echocardiographic findings described in the second echocardiogram performed are typical of cardiac amyloidosis.

An endomyocardial biopsy was performed to confirm the clinical suspicion. This demonstrated amorphous acellular material that separated myocytes (Figure 1) and displayed apple-green birefringence under polarized light after Congo Red staining.



**Figure 1.** Cardiac biopsy showing amorphous material (amyloid) between myocytes

Although serum/urine electrophoresis and immunofixation were normal and bone marrow biopsy did not show any dyscrasia, the patient was considered to have primary amyloidosis. He was discharged and followed at the outpatient clinic.

Two years later and after several admissions due to heart failure, the patient was transferred to our institution to consider heart transplantation. At our centre his echocardiogram now showed severely depressed left ventricular function (20%), his 6 minutes walking test was 310 metres, NT-proBNP was 4212 pg/ml and right catheterisation parameters showed a low cardiac index with pulmonary artery systolic hypertension. Renal function was normal and there was no major involvement of other organs/systems by the disease.

In order to determine the type of amyloidosis, another endomyocardial biopsy was performed. Immunohistochemistry was positive for TTR amyloid and genetic analysis of the TTR gene was performed. A mutation leading to the substitution of Glutamic acid by Lysine in position 89 was found. This mutation has been previously described in a Japanese family which had amyloidotic polyneuropathy.



TTR familial amyloidosis is an autosomal dominant disorder with high penetrance due to the production of amyloid from a mutant transthyretin (TTR) protein. The onset occurs most commonly after the age of 40 and depending on the type of mutation, peripheral neuropathy or cardiomyopathy may predominate. Some patients may have autonomic neuropathy with diffuse visceral pains. Renal involvement is usually uncommon. This entity is endemic in some regions of Portugal, Sweden and Japan reaching a prevalence of 1:600. More than 100 different mutations have been described so far with the Val122Ile mutation being found in approximately 4% of the black population in the United States. As transthyretin is almost exclusively produced by the liver, liver transplantation removes the source of amylogenic protein. When advanced cardiac amyloidosis is present combined heart and liver transplantation is the only alternative for these patients.

### Treatment

After an electroneurographic study, which showed mild to moderate polyneuropathy, the patient was considered suitable for heart and subsequent liver transplantation. Heart transplantation was successfully performed (Figure 2) and during the following year he returned to NYHA functional class I. Endomyocardial biopsies performed to monitor cardiac rejection did not show TTR deposits. One year after heart transplant, liver transplantation was performed and the patient's liver was used for an alternative recipient (domino transplant). Unfortunately, the patient developed hepatic artery thrombosis and had to be retransplanted urgently 1 month later. Almost 4 years after his heart transplant, the patient is well.



**Figure 2.** Explanted Heart

### Conclusions:

Cardiac amyloidosis is a difficult diagnosis which should be always suspected in patients with suggestive extracardiac signs and symptoms. It is crucial to determine the type of amyloid to offer correct treatment. Treatment of cardiac amyloidosis is very complex and collaboration between physicians of different specialties is essential to achieve good results.

### References

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