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CLINICAL STUDY

Effect of immunosuppressive therapy in inflammatory cardiomyopathy: data from The Czech Inflammatory Cardiomyopathy Immunosuppressive Trial

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ABSTRACT

INTRODUCTION: The indications for specific treatment in the cases of inflammatory cardiomyopathy are based on limited data from several small clinical trials.

AIM: A comparison of the effect of two dose regimens of combined immunosuppressive therapy by adding them to conventional heart failure therapy and comparing them with conventional heart failure therapy alone in patients with inflammatory cardiomyopathy.

METHODS AND STUDY POPULATION: We enrolled 20 patients; mean age 46.10±7.33 years, duration of symptoms <6 months, LVEF ≤40 %, NYHA class II–IV, with biopsy-proven myocarditis. Patients were randomly separated into groups treated with immunosuppressive therapy in addition to conventional heart failure therapy or to a group treated with conventional heart failure therapy alone. Clinical and echocardiographic parameters were evaluated.

RESULTS: The baseline values of LVEF in the group of immunosuppressive therapy (LVEF 22.3±4.7 %) were similar to those in the group treated with conventional heart failure therapy (LVEF 21.7±4.7 %; p=0.757). After twelve months there was no statistically significant difference in LVEF between the two studied groups (LVEF 33.7±9.5 % for the immunosuppressive therapy group and 41.3±13.0 % for the conventional therapy group; p=0.175).

CONCLUSION: In our study population, we proved no positive effect of combined immunosuppressive therapy on the left ventricular function over 12 months. The main limitation of the study is the small number of enrolled patients *(Tab. 4, Fig. 1, Ref. 35)*. Text in PDF *www.elis.sk*

KEY WORDS: myocarditis, inflammatory cardiomyopathy, endomyocardial biopsy, immunosuppressive therapy.

Introduction

Myocarditis is a disease characterized by inflammatory changes in the heart muscle. Inflammatory cardiomyopathy (ICM) is myocarditis with myocardial dysfunction (1). A transition from acute inflammation to subacute and chronic stages with left ventricle remodeling, fibrosis and loss of contractile myocardial function leading to dilated cardiomyopathy (DCM) were described in about 30 % of patients with myocarditis. DCM is one of the most common causes of chronic heart failure leading to heart transplantation, especially in young people (2). Inflammatory changes in the myocardium on EMB are detected in some patients considered to have DCM (3). The true incidence of the disease is difficult to determine due to the very wide spectrum of clinical symptoms and relatively complex diagnostic approach. A suspicion of the disease is expressed on the basis of noninvasive examinations, while the definitive diagnosis is based on myocardial biopsy (1). The original studies where the Dallas criteria were used for the diagnosis of myocarditis, reported a prevalence of myocarditis in 9–16 % of patients with DCM (4). Studies using immunohistochemistry for the diagnosis reported myocarditis in about 50 % of cases of DCM. According to the present registries, myocarditis affects especially young people (about 35–40 years old), mainly men (60–80 %). It is the cause of sudden cardiac death in young people in 6–10 % of cases (5, 6, 7, 8).

A wide spectrum of infectious and noninfectious agents can cause myocarditis. Viral infections are the most frequent causes of the disease in our region (7, 8, 9, 10). The clinical presentation is very diverse, from completely asymptomatic or mildly sympto-

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matic cases to cases with severe or fulminant heart failure. Sudden cardiac death can also occur in some cases (1, 3). The symptoms usually occur due to the dysfunction of the left ventricle while the heart failure symptoms are the most common clinical scenario in these patients. They can be mild, but in some patients with myocarditis, a cardiogenic shock can develop. The second form of clinical manifestation is chest pain that can mimic an acute coronary syndrome or may be a part of symptoms caused by potentially present perimyocarditis. The third form of presentation includes symptoms related to a wide spectrum of arrhythmias (11).

The diagnosis of myocarditis remains to be associated with difficulties. The diagnostic criteria postulated by The Position Statement of the ESC Working Group on Myocardial and Pericardial Diseases should be used (1). These criteria are based on clinical symptoms such as heart failure symptoms, chest pain and symptoms due to arrhythmias, and on noninvasive and invasive investigations. The most important noninvasive methods are echocardiography and magnetic resonance imaging, while the definitive diagnosis is based on endomyocardial biopsy (EMB) which is considered as the gold standard diagnostic method (1). The samples of the myocardium obtained by EMB are evaluated with histologic methods (Dallas criteria), immunohistochemistry (including cell typing) while the search for infectious agents is an integral part of the evaluation. Reverse polymerase chain reaction (PCR) is usually used for detecting the viral genome. The quantitative assessment of viral load (number of viral copies) should be done especially for PVB19, which is the most frequent virus detected in the myocardium in cases of myocarditis. The published data have shown that the low viral load (less than 500 copies/ug of genomic DNA) is not able to trigger myocarditis (11, 12). However the viral genome of PVB19 was detected also in the myocardium of patients with ischemic heart disease, valvular diseases and noninflammatory DCM, as well as in the healthy donor hearts used for heart transplantation (9, 13, 14).

More than half of the patients with acute myocarditis and initially impaired systolic function of the left ventricle (LV) show normalization of LVEF. In the remaining cases, a varying degree of systolic dysfunction is still present with progression to the picture of dilated cardiomyopathy. About 10–20 % of these patients progress to the terminal stage of heart failure and become candidates for heart transplantation (15). The course of the disease is influenced by many factors such as gender, genetic predisposition, grade of inflammatory response or viral genome persistence in the myocardium.

The therapy of myocarditis with systolic dysfunction is based on the guidelines for acute and chronic heart failure therapy (16, 17). In cases with a severe course of the disease leading to cardiogenic shock, left ventricular assist device implantation may be necessary as a bridge to recovery or transplantation (18).

A specific treatment of myocarditis is indicated based on the results of comprehensive evaluation of EMB samples. This treatment increases the chance of eliminating the infectious agents or possibly reducing or suppressing the autoimmune response and chronic myocardial inflammation. If bacterial infection, e.g., *Borrelia burgdorferi* is present, antibiotic therapy is indicated (15). The effect of antiviral therapy may be positive only at the beginning of the infection when the virus is replicating. However, myocarditis is usually diagnosed at the later stages of the disease when the virus replication is no longer present. The effect of antiviral therapy at this stage of the disease is already negligible. The immunomodulatory therapy with interferon-beta has been tested in cases where the viral persistence in the myocardium has been proven (19). The anti-inflammatory and antiviral effects of intravenous immunoglobulins have been tested and a positive effect has been proven in several small nonrandomized studies, while a randomized placebo-controlled study by McNamara did not confirm these results (20).

The immunosuppressive therapy is clearly indicated in the treatment of giant cell myocarditis, eosinophilic myocarditis and cardiac sarcoidosis (6, 21). Chronic lymphocytic myocarditis is the most common form (up to 90% of all myocarditis cases) of the disease, however the use of immunosuppression is still controversial in this subtype. Experiences are based on small, often monocentric observations or case presentations. If we omit the Myocarditis Treatment Trial by Mason which did not show a positive effect of combined immunosuppression in patients with myocarditis (4), only two randomized prospective studies demonstrating a positive effect of immunosuppressive therapy in ICM have been published. Wojnicz et al, and Frustaci et al investigated the effect of a combined immunosuppressive treatment administered for 3 to 6 months (23, 24). These studies investigated patients with symptoms lasting more than six months. All patients were treated with standard heart failure therapy, and they were randomized into groups which included immunosuppression or placebo in addition to conventional heart failure therapy. The immunosuppression consisted of steroids (prednisone) and azathioprine. The dosing scheme of immunosuppressive drugs and duration of the treatment were different in each study. Wojnicz and Frustaci reported a significant improvement in LVEF in the immunosuppressive group as compared to the placebo group within the studied period.

Methods and study population

The CZECH-ICIT study was planned as a prospective, randomized, multicentric study. The aim of this study was to compare the effect of two regimens of combined immunosuppressive therapy (azathioprine and prednisone) used in the above-mentioned studies (23, 24) on LV morphology and function in patients with biopsy-proven ICM and negative viral genome findings with the exception of PVB19 low viral load presence (less than 500 copies/ /ug genomic DNA). The duration of the heart failure symptoms should be shorter than 6 months (CZECH-ICIT 1) or longer than 6 months (CZECH-ICIT 2). The effect of combined immunosuppressive therapy in addition to conventional heart failure therapy and conventional heart failure therapy alone was compared.

The primary endpoint of the study was to compare the LVEF changes evaluated by echocardiography at a 12-month follow-up.

The secondary endpoints have been set as follows: changes in systolic and diastolic LV diameters; changes in NYHA heart failure classification; all-cause mortality; occurrence of the combined

endpoint consisting cardiovascular mortality, heart transplantation, hospitalization for heart failure, successfully resuscitated cardiac arrest and adequate ICD therapy for ventricular tachycardia or fibrillation; changes in the number of infiltrating inflammatory cells in baseline and control EMB samples; tolerance of therapy and incidence of adverse events as compared between both groups.

The CZECH-ICIT study was approved by the Ethics Committee of St. Anne´s University Hospital in Brno and all enrolled patients signed an informed consent form to enter the study.

Inclusion criteria: male and female patients with ICM, age 18–65 years old, LV systolic dysfunction (LVEF ≤40 %) lasting for at least 2 weeks and or at most 6 months since the onset of symptoms (CZECH-ICIT 1) or more than 6 months since the onset of the symptoms of heart failure (CZECH-ICIT 2), symptoms of heart failure NYHA class II – IV in patients with biopsy confirmed myocardial inflammation proven by immunohistochemistry (which means > 7 CD3+ lymphocytes/mm^2 and/or > 14 infiltrating leukocytes - LCA+ cells) with the exclusion of the presence of infectious agents – enteroviruses, adenoviruses, herpetic viruses, and bacteria *Borrelia Burgdorferi* (evaluation using polymerase chain reaction – PCR). The presence of PVB19 in low viral load was allowed.

Patients meeting the inclusion criteria were treated with conventional heart failure treatment based on the ESC Guidelines (including ACEI or ARB, betablockers and spironolactone) for at least 2 weeks before randomization. The study medication consisted of combined immunosuppression (azathioprine and prednisone).

In the first arm (R1), prednisone was administered for 90 days, while the initial dose was 1 mg/kg/day for 12 days, followed by a decreased dose, i.e., every 5 days the dose was reduced by 5 mg/day down to 0.2 mg/kg/day. Azathioprine was administered at a dose of 1mg/kg/day for 100 days.

In the second arm (R2), prednisone was administered for 6 months, initially at a dose of 1mg/kg/day for 4 weeks, followed by a dose of 0.33 mg/kg/day for the remaining 5 months. Azathioprine was administered for 6 months at a dose of 2 mg/kg/day. Immunosuppression was added to an already established heart failure treatment. In the third arm, the patients were treated with conventional heart failure therapy alone.

Adverse events of the therapy were monitored throughout the study. The possible adverse events were as follows: new onset or destabilization of diabetes mellitus, destabilization of hypertension with a necessity to change therapy, symptomatic osteoporosis, new onset or destabilization of peptic ulcer, clinically relevant changes in laboratory findings, infection, bleeding or significant increase in body weight.

Endomyocardial biopsy was performed at the baseline and at 6 months. Myocardial samples were taken from the right ventricle.

Statistical analysis

The main outcomes were presented as means and standard deviations (SD). The mean outcomes were compared at the baseline using a two-sided t-test to see if there was a significantly different outcome at the baseline that needed to be considered separately. All outcomes were analyzed using linear mixed models with a repeated structure of the matrix. The main studied fixed effect was the difference between the studied groups and the additional effects considered were time and a covariate that combines time with a group effect to study and observe a potential change in trend. The Kenward-Roger's approximation for degrees of freedom correction was used due to the small sample size. A significance level of 0.05 was considered and all tests used were two sided. Statistical software SAS 9.4 was used for all analyses and graphs.

A detailed design of the study has been published previously (15).

Results

Twenty patients were enrolled in the study, 18 men and 2 women of mean age 46.1 ± 7.3 years. More detailed characteristics of the study population are described in Table 1. All these patients had symptoms for less than 6 months and they were stabilized on standard heart failure therapy for at least 2 weeks (CZECH-ICIT 1). Before entering the study, they underwent endomyocardial biopsy and the myocardial samples were comprehensively evaluated. These patients also underwent detailed echocardiographic examination and selective coronarography to rule out significant stenosis of the coronary arteries. Basic laboratory tests were performed including troponin T and NT-proBNP. Detailed anamnestic data were obtained with evaluation of possible contraindications to immunosuppressive therapy. The NYHA class evaluation was performed in each study subject. Further control examinations were done at visits after 1, 3 and 6 months. Control EMB was performed after sixth months, while the final visit was done 12 months after randomization. After enrolling 20 patients, a descriptive interim analysis I was performed.

Due to the small number of patients enrolled in arm 2 (R2) – only 3 patients – the final analysis compared a group of patients treated with combined immunosuppression (regardless of the scheme) in addition to the conventional heart failure therapy and that of patients on conventional heart failure therapy only. After evaluating the interim results, no significant difference was found in the change of LVEF between the studied groups, which was the primary endpoint. This fact led to the cessation of further enrollment of patients into the study.

Tab. 1. The basic characteristics of the study population.

Parameter	Immunosuppression + heart failure therapy (IS+)	Heart failure therapy (IS-)	p
Number of patients	9	11	
NYHA classification	2.2±0.4	2.1±0.3	0.58
LVEF±SD (%)	22.3±4.7	21.7±4.0	0.76
EDd±SD (mm)	64.0±8,9	64.8±7.0	0.83
EDs±SD (mm)	57.1±7.9	57.9±6.2	0.33
Number of LCA positive cells±SD/mm^2	18.0±2,3	18.8±4.8	0.59
Number of CD3 positive cells±SD/mm^2	3.3±2.9	6.5±4.1	0.08

NYHA = New York Heart Association classification, LVEF = left ventricle ejection fraction, EDd = end-diastolic dimension, EDs = end-systolic dimension

Tab. 2. The changes in echocardiography parameters in 12 months.

Parameter	12M (IS+)	12M (IS–)	p
LVEF±SD (%)	33.7±9.5	41.3±13.0	0.18
EDd±SD (mm)	63.9±8.8	59.4±9.8	0.33
EDs±SD (mm)	53.9±10.6	49.0±10.2	0.33
NYHA classification	1.9±0.6	1.7±0.7	0.36

NYHA = New York Heart Association classification, LVEF = left ventricle ejection fraction, EDd = end-diastolic dimension, EDs = end-systolic dimension

Tab. 3. The changes in the number of infiltrating cells in EMB samples in 6 months.

Parameter	12M (IS+)	12M (IS–)	p
Number of LCA positive cells±SD/mm^2	9.8±5.5	9.9±4.2	0.21
Number of CD3 positive cells±SD/mm^2	2.3±2.2	2.8±1.0	0.70

Statistical analysis at the 12-month control showed results as follows: LVEF (the primary endpoint) increased in both studied groups, but there was no significant difference in LVEF between the groups. The baseline value of LVEF for patients treated with conventional heart failure therapy was 21.7±4.7 %, for patients treated with immunosuppression 22.3±4.7 % (p=0.757). After 12 months, LVEF increased to 41.3±13.0 % for conventional therapy and 33.7±9.5 % for immunosuppression (p=0.180) (Tab. 2). The p-value based on the t-test at twelve months was p=0.175 due to huge variability. The results obtained based on linear mixed models showed a trend that needs to be considered (Fig. 1). At the baseline there was a slightly lower value of LVEF in the conventional therapy group (estimate of difference 0.6, p=0.879), but the trend was changing over time and at 12 months there was a higher value of LVEF in the conventional therapy group (estimate of difference 11.4, p=0.008). The total p-value difference based on the adjusted F-test obtained for the group was p=0.065, for time p <0.0001 and for time*group p=0.537.

Similar results were obtained for the secondary endpoints. The development of echocardiography parameters and NYHA classification is shown in Table 2. It is necessary to mention that the numbers of infiltrating cells decreased in the myocardial samples in the control EMB over sixth months in both groups, but again, no significant difference between groups was found. In the baseline EMB there were 18.0±2.3 LCA+ cells in the conventional therapy group and 18.8±4.8 LCA+ cells in the immunosuppression-treated group (p=0.590). In the control myocardial samples at six months there were 9.9±4.2 LCA+ cells in the conventionally treated patients and 9.8±5.5 in the immunosuppression-treated group (p=0.70). The baseline number of CD3+ cells was 6.5±4.1 in the conventional therapy group while in the immunosuppression group, it was 3.3±2.9 (p=0.080). After six months, the number of CD3+ cells decreased to 2.8±1.0 cells for conventional therapy and to 2.3±2.2 for the immunosuppression group (p=0.210) (Tab. 3).

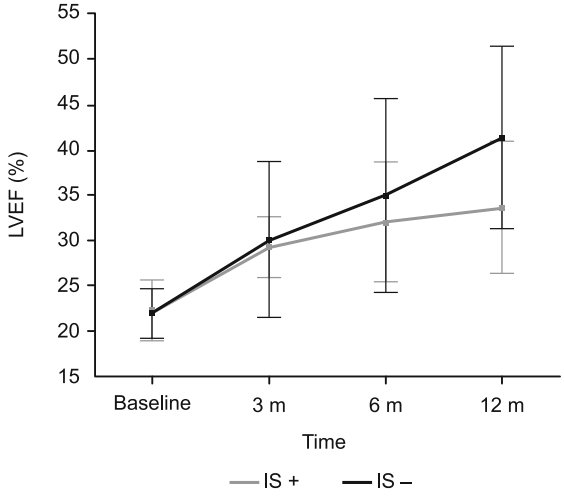

Fig. 1. The development of LVEF in 12 months.

Tab. 4. Side effects of the therapy.

Side effect	Number of patients (IS+)	Number of patients (IS–)
Diabetes mellitus	0	2
Hypertension	2	1
Osteoporosis	0	0
Peptic ulcer	1	0
Leukopenia	0	0
Anemia	0	0
Infection	1	1
Liver enzymes elevation	1	1

Other evaluated parameters were adverse events of the therapy. There was no significant difference between the treated groups in adverse events. In the immunosuppression group there were new onsets of diabetes in two patients, one patient had a newly diagnosed hypertension while in one patient, a serious infection was diagnosed. A significant elevation of liver enzymes was detected in one study subject. Similar adverse events were detected also in the conventional therapy-treated group. Two patients developed arterial hypertension. Peptic ulcer occurred in one patient, one patient had a more serious infection, and just like in the immunosuppression group, in one patient, an elevation of liver enzymes was detected. The comparison of the side effects of the therapy are shown in Table 4. During the study, one death from a non-cardiovascular cause occurred in the immunosuppression-treated group (generalized cancer of unknown origin) and one patient from this group was admitted to hospital for a new onset of atrial fibrillation. One patient from the conventional therapy group was hospitalized for the worsening of heart failure and treated with heart transplantation.

While the patients with a low viral load of PVB19 (less than 500 copies/ug of DNA) in the myocardium were enrolled in the study, one of the most interesting results of our study was associated with the monitoring of changes in PVB19 load in the control EMB. We did not see an increase in the number of viral DNA copies in any of control myocardial samples over six months in our small study group (only 9 patients with a low viral load of PVB19).

Discussion

Myocarditis and inflammatory cardiomyopathy are frequent causes of the development of dilated cardiomyopathy and heart failure. Despite advances in diagnostic methods, myocardial inflammation is still difficult to diagnose. The current treatment of myocarditis is predominantly symptomatic. The treatment is based on conventional heart failure therapy and treatment of arrhythmias according to established guidelines. Since the nature of myocarditis lies in exacerbated inflammation with features of autoimmunity, a positive effect of immunomodulation and immunosuppression may be expected. The immunosuppressive therapy is clearly indicated in some specific subtypes of myocarditis defined by myocardial biopsy findings (giant cell myocarditis, eosinophilic myocarditis, cardiac sarcoidosis and myocarditis associated with known extracardiac autoimmune disease) (25, 26, 27). In cases of lymphocytic myocarditis, the indication for the use of immunosuppressive therapy is still unclear. According to current recommendations, the immunosuppressive therapy may be used in patients with biopsy-proven myocardial inflammation, with the exclusion of infectious agents in the myocardium with persisting or worsening symptoms of heart failure despite conventional heart failure therapy, in patients with serious ventricular arrhythmias due to electrical instability, or in cases of recurrent myocarditis without contraindication for immunosuppression (1, 28). In line with other recently published studies, our data showed that the isolated presence of PVB19 at a low viral load in the myocardium of patients with myocardial inflammation does not have to be a contraindication for immunosuppressive therapy (10, 21, 22). In the donor hearts used for transplantation, the PVB19 genome was found in a similar percentage as in patients with myocardial inflammation. Although an aggressive immunosuppressive therapy after transplantation was used, we did not notice the development of myocarditis or rejection. Moreover, we also found no increase in the number of viral DNA copies in the repeated EMB (22, 29). Tschöpe et al noticed an effect of immunosuppressive therapy in patients with myocarditis with PVB19 presence that was similar to that in patients with myocarditis without genome PVB19 presence (27).

The data published on the prognostic benefit of immunosuppressive therapy are conflicting while a meta-analysis of published studies showed no prognostic benefit. On the other hand, a retrospective study by Merken et al suggests the possibility of a positive effect of such therapy on long-term survival (28, 30, 31). To date, there has been no large prospective, multicentric randomized study bringing clear data for unambiguous decision about the use of immunosuppressive treatment in ICM carried out. The data in this area are mainly based on the results of previous studies that were often retrospective or heterogenous in inclusion criteria, type of immunosuppressive protocol, duration of symptoms and follow-up period. Only two randomized prospective placebo-controlled studies in patients with lymphocytic myocarditis treated with combined immunosuppression have been published to date.

Wojnicz et al published a study with combined immunosuppressive therapy in ICM in 2001 (23). The study enrolled 84 patients with DCM while myocardial inflammation was proven by EMB and defined by an increase in the expression of HLA antigens. The evaluation of infectious agents present was not investigated. The primary endpoint comprised a composite of death, heart transplantation and hospital readmission for heart failure. After two years there were no significant differences in the primary endpoint. In the secondary endpoints there were significant differences between the studied groups; LVEF, LV diameters and volumes improved significantly in patients treated with immunosuppression after three months of this therapy and the improvement persisted at the 2-year follow-up as compared with the group without immunosuppression. Functional classification of NYHA also significantly improved in the group treated with immunosuppression as compared with the placebo group (23).

The second study in the field, namely the TIMIC trial by Frustaci et al, included 85 patients (24). The diagnosis was confirmed by EMB, myocardial samples were evaluated by immunohistochemistry, and viral genome presence was excluded by PCR testing. The primary endpoint was the improvement of LVEF after 6 months. In the group treated with immunosuppression, the increase in LVEF was significantly higher and the LV diameters and volumes were significantly more reduced in the immunosuppression treated group. In the placebo group, these parameters have even worsened. The difference between the two groups was significant (24).

Both published studies investigated the usefulness of a combined immunosuppressive therapy (azathioprine and prednisone) in patients with DCM with biopsy-proven inflammatory changes in the myocardium. These studies investigated patients with symptoms lasting more than six months. In each study there were different definitions of myocarditis, and different dosing schemes of immunosuppressive therapy were used. Both studies confirmed an improvement in LVEF, decrease in LV volumes and diameters in patients randomized to the immunosuppressive therapy group (23, 24).

Despite the data from these studies showing a positive effect of immunosuppressive therapy on ICM with symptoms lasting more than 6 months, one could speculate that the positive effect of immunosuppression on LV morphology and function might be even more pronounced had this therapy been administered earlier (less than 6 months from the onset of symptoms) by influencing LV remodeling at an early stage of disease. Therefore, our work was focused on this direction.

The hypothesis was that an early intervention with immunosuppression could reduce irreversible myocardial damage, especially fibrosis and myocardial remodeling. On the contrary, the immune response to the initial injury may help clear the virus and accelerate recovery in acute myocarditis. Consistently with this, it was frequently observed that there was a spontaneous improvement in LV function in patients with acute myocarditis. Moreover, the effect of immunosuppression could be more effective in the cases of overshoot of the immune response, e.g., in fulminant myocarditis. It is not clear if immunosuppressive therapy in a non-fulminant form of myocarditis could be effective in the acute phase. The results of previous clinical trials of immunomodulatory therapy in acute but non-fulminant myocarditis were ambiguous, but most

of them have demonstrated no benefit (4, 21). In contrast, persistent immune activation following the acute phase of myocarditis is associated with poor prognosis, and several trials of immunomodulatory therapy in chronic myocarditis have demonstrated an improvement in LVEF and functional class (23, 24, 32). Based on the results of our study one may even speculate that in the case of a larger number of included patients and with long-term follow-up there would be a trend to a higher value of LVEF in patients treated with conventional therapy.

As regards the mechanisms of action of the immunosuppression used in majority of the studies including our trial, it can be stated that prednisolone inhibits leukocyte extravasation and reduces macrophage phagocytic functions and production of TNF-alfa, IFN-gama, IL-1 and IL-2. Azathioprin is a prodrug metabolically activated to 6-mercaptopurine, the forms of which masquerade purine nucleotides, cytotoxic to activated lymphocytes (33, 34, 35).

Our study was originally conceived as a multicentric study aimed to compare two different regimens of immunosuppressive therapy used in previous studies (23, 24) by adding them to conventional heart failure therapy and comparing them with conventional heart failure therapy alone in patients with ICM.

In addition, we wanted to compare the use of this therapy in patients with symptoms lasting less than 6 months (CZECH-ICIT 1), where the evidence is extremely limited or even missing, and in patients with symptoms lasting more than 6 months (CZECH-ICIT 2; see the scheme). On the basis of the interim analysis I, a significant difference in primary endpoint between the study groups was not found and therefore the enrollment of patients in all three arms of the study was stopped. While all patients enrolled in the study had symptoms for less than 6 months, they were followed in a substudy (CZECH-ICIT 1). Despite the neutral result of our study, we consider the data obtained for immunosuppressive treatment in biopsy-proven myocarditis as being valuable especially in two respects. Immunosuppressive therapy was used for the first time in patients with biopsy-proven myocarditis and low viral load of PVB19. It is a very interesting finding in our study that despite immunosuppressive therapy, no increase in the viral load was observed in the control biopsy samples. The second important point of this study is that our patients had short-term symptoms, i.e., for less than 6 months. Although the results showed no benefit of immunosuppressive therapy, we believe that the obtained data could extend the existing knowledge in this area.

Conclusion

It can be summarized that in a population of patients with a new onset of inflammatory cardiomyopathy with symptoms lasting for less than 6 months, we confirmed no positive effect of combined immunosuppressive therapy on changes in LVEF at 12 months when added to conventional heart failure therapy and compared with conventional heart failure therapy alone. No significant differences were found in other parameters either. In patients with initial PVB19 presence in the myocardium, the immunosuppressive therapy led to no increase in the viral load in control EMB samples. The overall outcome of the study was influenced by the small number of enrolled patients. This underlines the need for a large multicenter prospective study that could remove the existing therapeutic uncertainty in this area.

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