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Acute inflammatory cardiomyopathy: apparent neutral prognostic impact of immunosuppressive therapy

The real efficacy and indication of immunosuppressive therapy (IST) in acute (i.e. <6 months) inflammatory cardiomyopathy (IC) due to lymphocytic myocarditis remain debated. Available data are controversial because they are derived from trials on chronic IC[1–3] or investigating immunomodulation in chronic viral cardiomyopathy,[4] or from observational studies including acute and chronic IC patients with short-term follow-up.[5] The aim of this study was to assess the prognostic impact of IST in a population of acute IC patients.

Methods

We analysed retrospectively all patients with acute (i.e. <6 months) left ventricular systolic dysfunction and an indication for endomyocardial biopsy (EMB) consecutively admitted at the Cardiovascular Department of Trieste, Italy, between 2000 and 2018. According to recent international statements,[6] the indications for EMB and potentional use in IC include: (i) unexplained heart failure with left ventricular ejection fration (LVEF) <40%, refractory to conventional treatment in the short term; (ii) unexplained major ventricular arrhythmias (MVAs) associated with LVEF <50%. Inflammatory cardiomyopathy was defined as the presence of EMB-proven myocarditis with LVEF <50%.[2] IST consisted of prednisone (50 mg/m^2/day with progressive

Table 1 Characteristics of inflammatory cardiomyopathy patients treated and not treated with immunosuppressive therapy

	Total (*n* = 65)	IST (*n* = 34, 52.3%)	No IST (*n* = 31, 47.7%)	*P*-value
Age (years)	46 ± 17	46 ± 19	46 ± 14	0.859
Male sex	36 (55.4)	20 (58.8)	16 (51.6)	0.559
Duration of symptoms (days)	58 [20–140]	58 [23–175]	55 [18–115]	0.451
Admission SBP (mmHg)	112 ± 18	110 ± 15	115 ± 20	0.549
NYHA class				
II	17 (26.2)	7 (20.6)	10 (32.3)	0.219
III	16 (24.6)	10 (29.4)	6 (19.4)	0.397
IV	12 (18.5)	9 (26.5)	3 (9.7)	0.093
Fulminant form	7 (10.8)	5 (14.7)	2 (6.5)	0.638
Presentation with HF	37 (56.9)	24 (70.6)	13 (41.9)	0.016
Atrial fibrillation	2 (3.1)	0 (0)	2 (6.5)	0.196
QRS length (ms)	103 ± 31	98 ± 30	109 ± 31	0.273
LVEDVi (mL/m^2)	83 ± 25	84 ± 22	82 ± 27	0.733
Baseline LVEF (%)	30 ± 9	29 ± 7	31 ± 11	0.554
LVEF at discharge (%)	34 ± 10	33 ± 8	34 ± 11	0.723
LAESAi (cm^2/m^2)	14 ± 4	14 ± 4	14 ± 5	0.823
RVD	18 (27.7)	8 (23.5)	10 (32.3)	0.515
Moderate to severe MR	20 (30.7)	10 (29.4)	10 (32.3)	0.666
RFP	22 (33.8)	10 (29.4)	12 (38.7)	0.643
Poor lymphocytic infiltrate	48 (73.8)	17 (50)	31 (100)	<0.001
Moderate to severe fibrosis at EMB	40 (61.5)	19 (55.9)	21 (67.7)	0.337
PCR virus-positive at EMB	13 (20)	6 (17.6)	7 (22.6)	0.166
Beta-blockers at discharge	55 (84.6)	28 (82.4)	27 (87.1)	0.962
ACEi/ARBs at discharge	59 (90.8)	31 (91.2)	28 (90.3)	0.286
Aldosterone receptor antagonists at discharge	34 (52.3)	18 (27.7)	16 (51.6)	0.818
Diuretics at discharge	45 (69.2)	24 (70.6)	21 (67.7)	0.524
LVRR at 24 months	31 (67.4)	19 (70.4)	12 (63.2)	0.607

Values are expressed as mean ± standard deviation, *n* (%), or median [interquartile range].
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AV, atrioventricular; EMB, endomyocardial biopsy; HF, heart failure; IST, immunosuppressive therapy; LAESAi, left atrial end-systolic area index; LBBB, left bundle branch block; LVEDD, left ventricular end-diastolic diameter; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVRR, left ventricular reverse remodelling; MR, mitral regurgitation; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; PCR, polymerase chain reaction; RFP, restrictive filling pattern; RVD, right ventricular dysfunction; SBP, systolic blood pressure.

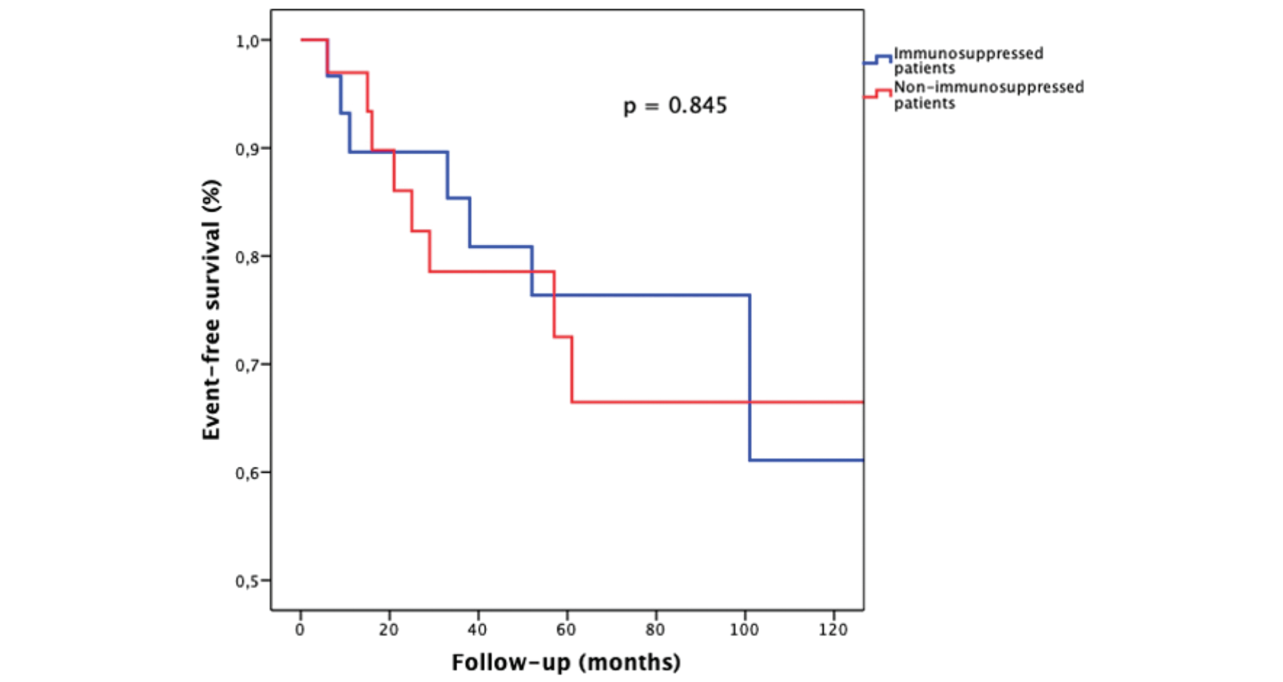

Figure 1 Kaplan–Meier curves: long-term neutral impact of immunosuppressive therapy on acute inflammatory cardiomyopathy in terms of death, heart transplant, or major ventricular arrhythmias.

downscaling) and azathioprine (75 mg/m^2/day) for at least 6 months. IST was administered on top of conventional treatment in the presence of all of the following: (i) myocardial immune activation at immunohistochemistry analysis (using a large panel of monoclonal and polyclonal antibodies including anti-CD3, T lymphocytes; anti-CD68, macrophages; and anti HLA-DR); (ii) absence of viral genome in cardiomyocytes (or presence of <250 copies/µg DNA of parvovirus B19[5]) by real-time polymerase chain reaction (PCR). Only IC due to lymphocytic myocarditis was considered.

The study outcome measure was a composite of all-cause death or heart transplant (D/HTx) or MVAs (i.e. sustained ventricular tachycardia, ventricular fibrillation, appropriate intervention of implanted cardioverter-defibrillator). Moreover, left ventricular reverse remodelling (LVRR) at 24 (range 9 to 36) months, defined as a LVEF increase ≥10 points associated with a left ventricular end-diastolic diameter decrease ≥10%,[6] was evaluated.

Results

The study population included 81 patients (45 ± 16 years, 59% male; LVEF 29 ± 10%). The IC group included 65 (80.2%) patients. In the IC group, IST was administered in 52% (*n* = 34) of patients. Notably, 13 patients had a positive specimen for viral PCR, all with low levels of parvovirus B19, and six of them received IST. Descriptive analysis (*Table 1*) showed no significant differences between patients treated and not treated with IST, except a higher rate of poor lymphocytic infiltrate at EMB in non-treated patients. At 24 months, LVRR was found in 19 IST (70.4%) vs. 12 (63.2%) non-IST patients ($P = 0.607$; *Table 1*). At Kaplan–Meier analysis, during a mean follow-up of 144 ± 12 months, no differences in D/HTx/MVAs rates were found between IST and non-IST patients (23.5% vs. 22.6%; $P = 0.845$; *Figure 1*).

Discussion

This is the first study that evaluates the impact of IST in a well-characterized cohort of only acute IC patients. The main findings are: (i) the prevalence of IC is very high (80%) when biopsy-proven diagnosis is guided by clinical suspicion, according to current international statements[6]; (ii) the very long-term impact of IST appears neutral in acute IC. Having a high percentage of positive biopsy-proven diagnosis of IC is fundamental due to a mild, but not negligible, rate of major complications of the procedure.[6] Moreover, from our results, we might argue that IST in acute IC could not impact on LVRR and long-term survival. However, the retrospective nature, the small sample and the long enrolment period are relevant limits of this study and do not allow to derive an absolute negative conclusion about the efficacy of IST in this setting. The high rate of poor lymphocytic infiltrate in IST patients might help to identify specific indications for IST.[7] It clearly emerges the need for new prospective randomized trials aimed at clarifying the role of IST in patients with biopsy-proven acute IC.

Conflict of interest: none declared.

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