Clinical effects of cyclosporine in acute anterior myocardial infarction complicated by heart failure: A subgroup analysis of the CIRCUS Trial

Although much progress has been made in the treatment of patients with ST-segment elevation myocardial infarction (STEMI), the rates of death and heart failure remain high, particularly in the subgroup of patients with large infarctions presenting with hemodynamic instability (Killip class ≥2).[1-3] The present study explored the effects of cyclosporine (cyclosporin A, CsA), a drug with potential infarct size−reducing and anti-inflammatory effects, on infarct size and on clinical outcome in patients with acute myocardial infarction (AMI) complicated by heart failure. Although the overall effect of cyclosporine was neutral in the Does Cyclosporine Improve Clinical Outcome in ST Elevation Myocardial Infarction Patients (CIRCUS) trial,[4], there was a significant interaction between Killip class and treatment effect ($P = .009$), suggesting a beneficial effect of CsA in the subgroup of patients with AMI complicated by heart failure.

Methods

The present substudy of the CIRCUS trial focused on 97 patients with a Killip class ≥2 (out of the 791 patients included in the primary endpoint analysis of the CIRCUS study). The CIRCUS trial was an academic, international, multicenter, prospective, double-blinded trial targeting patients with an acute anterior infarction and with the presence of an occluded left anterior descending artery at the time of percutaneous coronary intervention (PCI).[4,5] The investigational product was a lipid emulsion formulation of cyclosporine (CicloMulsion, NeuroVive Pharmaceutical) administered intravenously at a dose of 2.5 mg/kg of body weight shortly before revascularization by PCI. In total, 49 patients received CsA prior to PCI, whereas 48 patients were allocated to the placebo arm.

Clinical outcomes included worsening of heart failure during initial hospitalization, and a composite end point of worsening of heart failure during the initial hospitalization or rehospitalization for heart failure or all-cause death at 1 year. Worsening heart failure should include intravenous treatment with a diuretic, inotropic, or vasodilating agent. We also looked at the development of cardiogenic shock during initial hospitalization and during follow-up. *Cardiogenic shock* was defined as the presence of systolic blood pressure <80 mm Hg for >30 minutes that was unresponsive to fluid replacement and was associated with signs of peripheral and end-organ hypoperfusion.

Clinical outcomes were evaluated by using mixed-effects logistic regressions that included treatment as a fixed effect and center as a random effect. Adjusted risk estimates were obtained using a Cox proportional-hazards model including all univariate predictors at $P < 10\%$ or deemed to be clinical relevant and proportional-hazards hypothesis as checked. Ultimately, multivariate model was adjusted only on age, final Thrombolysis in Myocardial Infarction flow, diabetes, ejection fraction, baseline creatine kinase (CK), multivessel disease and Killip at admission. A log transformation was done for non-normal variables. All adverse clinical events were adjudicated by an independent event validation committee. The Rentrop score and area at risk according to angiography were determined as previously described.[4]

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

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Results and discussion

There were no significant differences between the 2 study arms, but there was a trend for higher Killip class and more proximally located coronary artery occlusion in the control group (Table I). Patients treated with CsA showed comparable rates of successful reperfusion (ST-segment resolution of >70%), had comparable infarct sizes (peak median total CK release 4069 U [IQR 2737-6132] in CsA vs 4791 U [2990-6537] in control), and had borderline better left ventricular ejection fractions during index hospitalization (43 ± 10.3 vs 38.4 ± 13.5, $P = .041$) and at follow-up (42 ± 11 vs 33 ± 22, $P = .16$).

Worsening of heart failure during index hospitalization occurred in 26% of the patients in the treatment arm and in 44% of the patients in the placebo arm ($P = .08$). Progression from Killip class 2/3 to cardiogenic shock during index hospitalization occurred in 6% of the patients in the treatment arm and in 12% of the patients in the placebo arm ($P = .47$). The composite endpoint at 1 year occurred less frequently in the cyclosporine arm than in the control arm (35% vs 58%, $P = .02$, log-rank $P = .03$) (Table II). However, after adjustment for the baseline characteristics, cyclosporine was no longer associated with improved clinical outcome (adjusted HR: 0.68 [0.3−1.4]) (see also Supplemental Table). Most likely, suboptimal matching of the study groups, with the presence of more jeopardized myocardium in the control

Table I. Characteristics of the patients

Characteristics	Cyclosporine (n = 49)	Control (n = 48)	*P* value
Age, y	63.7 ± 14.4	59.4 ± 12.9	.434
Male sex, n (%)	35/49 (71.4%)	513/607 (84.5%)	.947
BMI	27.1 ± 4.4	26.7 ± 4	.474
Current smoking, n (%)	21/49 (42.9%)	17/48 (35.4%)	.587
Hypertension, n (%)	21/49 (42.9%)	29/48 (60.4%)	.127
Diabetes mellitus, n (%)	10/49 (20.4%)	13/48 (27.1%)	.593
Dyslipidemia, n (%)	22/49 (44.9%)	24/48 (50%)	.764
Previous myocardial infarction, n (%)	4/49 (8.2%)	3/48 (6.2%)	.999
Previous coronary artery disease, n (%)	3/49 (6.1%)	7/48 (14.6%)	.199
Previous heart failure, n (%)	1/49 (2%)	2/48 (4.2%)	.617
Baseline plasma total CK (IU/L)	223 (134–877)	349 (131–1602)	.340
Killip class at admission, n (%)			.267
II	42/49 (85.7%)	35/48 (72.9%)	
III	5/49 (10.2%)	8/48 (16.7%)	
IV	2/49 (4.1%)	5/48 (10.4%)	
Total ischemic time, h	3.8 (2.7–5.4)	3.8 (2.3–5.3)	.713
LAD occlusion site, n (%)			
Proximal or main left artery	26/49 (53.1%)	31/48 (64.6%)	.344
Area at risk, %	37.9 ± 8.6	40.1 ± 7.6	.316
Rentrop score >1, n (%)	2/48 (4.2%)	4/47 (8.5%)	.435
TIMI flow grade 3 after PCI, n (%)	40/48 (83.3%)	36/47 (76.6%)	.645
Multivessel disease, n (%)	24/49 (49%)	17/48 (35.4%)	.252
Thrombus aspiration, n (%)	34/49 (69.4%)	39/48 (81.2%)	.263
Stenting, n (%)	46/49 (93.9%)	44/48 (91.7%)	.715
No reflow, n (%)	8/49 (16.3%)	2/48 (4.2%)	.091
IABP, n (%)	2/49 (4.1%)	2/48 (4.4%)	.999

Data are presented as the mean value ± SD, median (interquartile range), or proportion (%).
BMI, Body mass index; *IABP*, intra-aortic balloon pump; *LAD*, left anterior descending artery; *MI*, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

Table II. Clinical outcome

	Cyclosporine (n = 49)	Control (n = 48)	OR (95% CI) Unadjusted
Composite outcome (death, HF)	17/49 (34.7%)	28/48 (58.3%)	0.38 (0.17-0.86)
All-cause death			
At 1 m	6/49 (12.2%)	3/48 (6.3%)	2.09 (0.49-8.9)
At 1 y	7/49 (14.3%)	9/48 (18.8)	0.77 (0.24-2.47)
Cardiovascular death			
At 1 m	5/49 (10.2%)	3/48 (6.3%)	1.7 (0.38-7.57)
At 1 y	6/49 (12.2%)	9/48 (18.8%)	0.65 (0.19-2.23)
HF	17/49 (34.7%)	25/48 (52.1%)	0.49 (0.22-1.11)
Worsening of HF	13/49 (26.5%)	21/48 (43.8%)	0.46 (0.2-1.09)
Rehospitalization of HF	9/49 (18.4%)	14/48 (29.2%)	0.55 (0.21-1.42)
Cardiogenic shock	4/49 (8.2%)	9/48 (18.8%)	0.39 (0.11-1.35)

HF, Heart failure.

group, favored the outcome in the CsA arm. The observed significant interaction found in the CIRCUS trial could be also just a play of chance. The lack of effect on infarct size and clinical outcome is consistent with the results of more recent clinical trials with cyclosporine and challenges the view that the mitochondrial permeability transition pore plays a role in reperfusion injury in humans.[6,7]

The results of this study should be considered in the context of the following limitation. As the CIRCUS trial did not follow a prespecified randomization according to Killip class, the matching of the 2 study groups was suboptimal. We have tried to overcome that limitation by applying Cox regression analysis, although unreported baseline characteristics might have influenced the outcome of the analysis.

In conclusion, the administration of CsA prior to PCI did not reduce infarct size and had no cardioprotective effect in acute anterior myocardial infarction complicated by heart failure. Novel therapies need to be tested to improve the prognosis of this high-risk patient population.

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