Immunosuppressive Therapy and Interferon-1β in Acute Myocarditis

Miocarditis aguda: experiencia con tratamiento inmunosupresor e interferón-1β

To the Editor,

Acute myocarditis is an inflammatory disease of the myocardium with a variable presentation and clinical course. Although the symptoms spontaneously resolve in between 50% and 60% of patients, 20% to 40% die or require heart transplantation.[1,2] Most patients with a favorable course improve during the first 2 to 4 weeks. A worse clinical course has been associated with the presence of ventricular dysfunction.[1–3]

From July 2008 to March 2016, 32 infants and children (0-16 years) with acute myocarditis were admitted to our center. Of these, 53% (17 of 32) had a left ventricular ejection fraction (LVEF) < 35%; 47% of these patients (8 of 17) died or required transplantation. Although acute myocarditis is definitively diagnosed with endomyocardial biopsy (EMB), the technique is not performed systematically because of some associated risks.[3] Some immunosuppressive or antiviral therapies can be useful in the subacute or chronic phase.[4–6]

Interferon-1β (IFN-1β) is a molecule secreted by immune system cells, mainly fibroblasts. Its serum levels are decreased in patients with myocarditis and persistent virus in the myocardium[6] and it is therapeutically useful in patients with dilated cardiomyopathy and polymerase chain reaction (PCR) detection of a viral genome.[5,6] In addition, immunosuppressive therapy can be useful in patients with inflammatory cardiomyopathy and negative viral PCR results.[4] Accordingly, from February 2015, a specific protocol-directed therapy was implemented in those patients in our center with acute myocarditis and LVEF < 35% with no echocardiographic evidence of improvement after 2 weeks. The suspected diagnosis was made according to clinical symptoms and suitable complementary examinations, including cardiac magnetic resonance imaging.[3] Before the therapeutic approach was chosen, EMB was performed in patients with an unfavorable clinical course. We performed histological and immunohistochemical studies and viral PCR analysis. Myocarditis was diagnosed by the presence of > 14 leukocytes with > 7 lymphocytes/mm^2.

Patients with inflammation and negative PCR were treated with methylprednisolone and mycophenolate mofetil for 6 months. Because mycophenolate has fewer adverse effects,[4] it was used instead of azathioprine. If a positive viral PCR result was obtained in the myocardium, treatment was begun with subcutaneous IFN-1β for 6 months (Betaferon at a dosage of 4 million units 3 days a week[5,6]) and specific antiviral treatment if available. Methylprednisolone was added if there was inflammatory infiltrate.

Here, we detail our experience with 4 patients. Their characteristics are shown in the Table. Three were transferred from other centers for transplant evaluation and the fourth was admitted with cardiogenic shock. All had severe involvement of the left ventricle with a mean LVEF at admission of 24.7% (SD: ± 7.3) and a mean left ventricular end-diastolic diameter Z score of 6.7 (SD: ± 3.4). The patient with cardiogenic shock required circulatory assistance with extracorporeal membrane oxygenation. In this patient, EMB was performed on the first day together with balloon atrial septostomy. In the remaining patients, EMB was performed 53 days (SD: ± 22) after diagnosis. The access was femoral in the patient with extracorporeal membrane oxygenation and jugular in the rest. The samples were obtained from the right side of the interventricular septum. There were no intraprocedural complications. Two patients had inflammation with negative PCR findings in the myocardium and peripheral blood; the other 2 had inflammation with positive PCR for the B19 parvovirus in the myocardium and peripheral blood. Specific therapy was begun after the EMB result. The mean LVEF before treatment was 26% (SD: ± 6). Currently, 3 patients have completed the therapy and the fourth has received it for 4 months. After a mean follow-up of 7 months (SD: ± 2.4), the mean ejection fraction was 55.2% (± 10.2%, P = .01). Two patients are now cured and 2 have improved, with some residual dysfunction. The 2 cured patients were infected with B19 parvovirus and were treated with IFN-1β. Regarding complications, the patients treated with IFN-1β showed increased transaminase levels (maximum AST/ALT values of 500/150 UI/L); the levels normalized after temporary withdrawal of the drug (5 days) and remained stable upon reintroduction of IFN-1β.

In conclusion, we consider that IFN-1β and immunosuppressive therapy can have beneficial results in patients with acute myocarditis. Endomyocardial biopsy is essential before treatment initiation. Prospective randomized multicenter studies are re-

Table
Baseline and Post Treatment Characteristics of the Patients

	1	2	3	4
Age at diagnosis, mo	26	26	36	26
Sex	F	M	F	M
Clinical symptoms	HF	HF	CS	CS
Supportive care	VDs	VDs	VDs	VDs + ECMO
LVEF at diagnosis	17	32	30	20
LVEDD at diagnosis, Z score	10.4	3	8.65	4.8
Time from diagnosis to EMB, d	39	32	76	0
Time from diagnosis to treatment, d	50	33	77	6
EMB	Inflammation	Inflammation	Inflammation	Inflammation
PCR of myocardium	Negative	Parvovirus	Parvovirus	Negative
PCR of blood	Negative	Parvovirus	Parvovirus	Negative
LVEF after 1 mo of treatment	34	35	50	52
Current LVEF	44	63	65	48
Current LVEDD, Z score	6.3	1.3	3	1.4

CS, cardiogenic shock; ECMO, extracorporeal membrane oxygenation; EMB, endomyocardial biopsy; F, female; HF, heart failure; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; M, male; PCR, polymerase chain reaction; VDs, vasoactive drugs.

quired to determine the usefulness of these treatments in pediatric patients.

Ferran Gran,[a,*] María Martínez-Villar,[b] Pere Soler-Palacín,[c] Aurora Fernández-Polo,[d] Pedro Betrián,[a] and Dimpna C. Albert[a]

[a]*Unidad de Cardiología Pediátrica, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain*
[b]*Servicio de Pediatría, Hospital Vega Baja, Orihuela, Alicante, Spain*
[c]*Unidad de Enfermedades Infecciosas e Inmunodeficiencias Pediátricas, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain*
[d]*Servicio de Farmacia, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain*

*Corresponding author:
E-mail address: fgranipina@gmail.com (F. Gran).

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Inverted *Tako-tsubo* Induced by Pheochromocytoma

Tako-tsubo *invertido provocado por feocromocitoma*

To the Editor,

Catecholamine-producing tumors have a low incidence and rarely involve myocardial toxicity. The inverted variant of *tako-tsubo* syndrome is uncommon and occurs in younger patients. ST-T depression is the most typical abnormality seen on electrocardiography. This variant is also associated with an increased incidence of cardiogenic shock, arrhythmias, and kidney failure.[1]

We describe the case of a 52-year-old woman with a history of chronic hypertension currently under treatment with enalapril. A recent echocardiogram showed no structural heart disease. She was admitted to the emergency service for sudden-onset severe headache and general malaise. At admission, blood pressure, electrocardiogram (Figure 1A), and chest X-ray were normal. During her stay in the emergency room, she developed disorientation, clouding of consciousness, and vomiting. Documented blood pressure was 210/100 mmHg. Blood test values were within normal limits and the results of cranial CT scan were unremarkable. Subsequently, the patient had a chest pain episode with ischemic features. Electrocardiogram was repeated and showed ST depression in V_5-V_6, II, III, and aVF (Figure 1B). An emergency echocardiogram showed moderate-severe ventricular dysfunction with preserved apical contractility (Video 1 of the supplementary material). Based on these findings, cardiac catheterization was performed with no evidence of obstructive lesions or vasospasm and with good coronary flow (TIMI III; Video 2 and Video 3 of the supplementary material). Ventriculography showed findings similar to those of the electrocardiogram and were compatible with inverted *tako-tsubo* syndrome (Figure 1C). Given the hypertensive crises, renal artery angiography was performed with no evidence of stenosis, but showed a vascular neoformation extending to the right upper renal pole (Figure 2A). Peak creatine kinase was 613 U/L and peak ultrasensitive troponin was 1707 ng/dL. Several hours after cardiac catheterization, the patient had another hypertensive crisis and hemodynamic deterioration requiring invasive mechanical ventilation, vasoactive support with noradrenaline at 1.1 μg/kg/min, dobutamine at 18 μg/kg/min, and intraaortic balloon counterpulsation (IABC). A new echocardiogram performed in the subcostal plane showed a mass of about 5 cm adjacent to the inferior vena cava (Figure 2B). An abdominal CT scan showed a right adrenal mass (Figure 2C). The patient remained hemodynamically unstable (cardiogenic shock and 2 episodes of ventricular tachycardia and cardiorespiratoy arrest), for which venoarterial extracorporeal membrane oxygenation (ECMO) was commenced with distal cannulation 24 hours after IABC. There was a stepped decrease in catecholamine levels. On the third day of circulatory support with ECMO, ventricular function recovered (Video 4 of the supplementary material), and so circulatory and vasoactive support were progressively withdrawn. Right adrenalectomy was performed after the patient was started on therapy with alpha-blockers and subsequently with beta-blockers. The pathologic findings (poorly differentiated necrotic cells) and the results of blood analysis (chromogranin A, 594 ng/mL [0-100]; metanephrine, 203 pg/mL [0-90], and normetanephrine, 414 pg/mL [0-180] in plasma) were compatible with pheochromocytoma.

We present a case of inverted *tako-tsubo* syndrome with cardiogenic shock, likely caused by a massive release of catecholamines due to pheochromocytoma. This phenomenon in association with pheochromocytoma was first described by a Spanish group in 2006.[2] The use of exogenous catecholamines during diagnostic tests could lead to false positives, and thus endogenous catecholamine levels should be determined after the withdrawal of vasoactive support and then compared after the tumor has been removed. In the present case, normal values were restored during follow-up. Various mechanisms of catecholamine-mediated toxicity have been proposed, such as excessive sympathetic stimulation, and increased inotropism, chronotropism, and afterload.[3] Alpha-adrenergic activation could cause vasospasm and direct myocardial toxicity via an increase in the permeability of the sarcolemmal membrane and in intracellular cardiac calcium concentrations.[4] Apical