

# Lupus Myocarditis: Initial Presentation and Longterm Outcomes in a Multicentric Series of 29 Patients

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**ABSTRACT. Objective.** Cardiac involvement during systemic lupus erythematosus (SLE) may include the pericardium, myocardium, valvular tissue, and coronary arteries. The aim of this study was to describe the clinical, biological, and radiological presentation of lupus myocarditis (LM) as well as the treatment response and longterm outcomes.

**Methods.** We conducted a multicentric retrospective study of LM from January 2000 to May 2014.

**Results.** Twenty-nine patients (3 men and 26 women) fulfilled the inclusion criteria (median age at the diagnosis of SLE: 30 yrs, range 16–57). Myocarditis was the first sign of SLE in 17/29 cases (58.6%). Troponin was elevated in 20/25 cases. Electrocardiogram results were abnormal in 25/28 cases. Echocardiography revealed low ( $\leq 45\%$ ) left ventricular ejection fraction (LVEF; 19/29, 66%) and pericardium effusion (20/29, 69%). Cardiac magnetic resonance imaging revealed delayed gadolinium enhancement in 9/13 patients (69%). Patients were treated with corticosteroids ( $n = 28$ ), cyclophosphamide (CYC;  $n = 16$ ), intravenous immunoglobulins ( $n = 8$ ), and/or mycophenolate mofetil ( $n = 2$ ). The median followup was 37 months. One month after the beginning of the treatment, 10/23 patients (43%) who had undergone echocardiography had an LVEF  $\geq 55\%$ . At the end of followup, 21/26 patients (81%) exhibited an LVEF  $\geq 55\%$ . Three patients died during followup, and 2 died from LM.

**Conclusion.** LM is a severe manifestation of SLE. It can be the first manifestation of the disease or it can occur during followup, in particular in untreated patients. However, the longterm prognosis is typically positive. Patients with less severe disease exhibited good LVEF recovery without CYC. (First Release November 15 2016; *J Rheumatol* 2017;44:24–32; doi:10.3899/jrheum.160493)

## Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS      LUPUS MYOCARDITIS      HEART FAILURE  
CARDIAC MAGNETIC RESONANCE IMAGING      LONGTERM OUTCOME

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Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder principally affecting young women and characterized by skin and hematologic manifestations, polyarthritis, renal involvement, and serositis. The heart may be involved in up to 50% of patients<sup>1</sup>. Although pericarditis is the most frequent manifestation of SLE-related cardiac disease, all other cardiac structures may be involved: endocardium, myocardium, conduction tissue, and coronary arteries.

Myocarditis in the setting of SLE requires urgent clinical attention because of the likely progression to arrhythmias, conduction disturbances, dilated cardiomyopathy, and heart failure<sup>2</sup>. Postmortem studies from the 1950s and 1960s reported myocarditis in 57% (72 of 126) of patients with SLE, indicating that subclinical myocardial involvement may commonly occur in such patients<sup>3,4</sup>. The current prevalence of lupus myocarditis (LM) has been estimated to be about 9% but tends to be lower in more recent studies<sup>5,6,7</sup>.

Myocarditis may exhibit a varied clinical presentation: dyspnea, fever, chest pain, and/or palpitations. Biological manifestations are nonspecific and may include the elevation of troponin. The gold standard for diagnosis confirmation remains endomyocardial biopsy (EMB)<sup>8,9</sup>. However, this procedure is not routinely used because of its low sensitivity and potential complications. Thus, myocarditis diagnosis is often achieved using clinical findings, biological markers, and imaging, classically echocardiography<sup>10</sup>. The use of cardiac magnetic resonance imaging (cMRI) in the diagnosis of myocarditis has been evaluated and appears to be efficient<sup>11</sup>.

The typical therapy for LM includes high-dose corticosteroids with or without other immunosuppressive therapy in addition to standard cardiac management<sup>6,7</sup>. Because SLE-related myocarditis is rare, there are few prospective studies, and management is based on isolated cases or small-series reports. Moreover, very few studies have noted the longterm outcomes and prognosis of this disorder, especially regarding cardiac recovery.

The aim of our study was to describe clinical, biological, and radiological features of LM, the treatment response, and longterm outcomes.

## MATERIALS AND METHODS

We conducted a retrospective, multicenter study from 3 French university hospitals. From January 2000 to May 2014, we identified from local databases patients with SLE who received a final diagnosis of LM. The study was conducted in compliance with the Helsinki Declaration guidelines: in accordance with the current French legislation (Loi Huriet-Serusclet 88-1138), declaration to a research ethics board is not needed for observational studies when disease management is unchanged.

**Inclusion and exclusion criteria.** Inclusion criteria were (1) patients with definite SLE according to the American College of Rheumatology classification criteria ( $\geq 4$  criteria) updated in 1997<sup>12</sup>; and (2) myocarditis defined by 2 or more of the following<sup>9</sup>: high serum troponin level according to the local laboratory normal values; new or worsening changes on echocardiography, including new wall motion abnormalities and impaired left ventricular ejection fraction (LVEF); and delayed gadolinium enhancement on cMRI in an epicardial and/or midwall myocardial pattern or new impaired LVEF.

Exclusion criteria were (1) patient with preexisting cardiac disease such as cardiomyopathy, congenital heart disease, or cardiac insufficiency; (2) coronary artery occlusion; (3) myocardial depression owing to severe septic shock; (4) multisystem organ failure; (5) catastrophic antiphospholipid syndrome at the time ventricular dysfunction occurred; or (6) lack of sufficient data in medical records.

All the troponin levels were determined with non-high-sensitivity troponin assays.

**Data collection and outcome.** Demographic, clinical, biological and imaging data as well as treatments were collected retrospectively through medical records. Baseline was defined as the time of myocarditis diagnosis. We also noted the length of stay at the hospital, intensive care unit (ICU) admission, deaths, and cardiac recovery during the followup.

**Patient followup.** Patients were treated and followed according to the clinical physician's habits. Followup ended July 31, 2014.

**Endpoints.** The primary endpoint was the LVEF recovery 1 month after baseline. LVEF was evaluated using echocardiography and was considered normal if  $> 55\%$ .

Secondary endpoints were LVEF recovery at any time during followup, as evaluated by echocardiography (LVEF  $\geq 55\%$ ), and relapse occurrence, defined by worsening of the LVEF and/or increase in troponin levels with exclusion of other causes of troponin elevation and/or new delayed gadolinium enhancement on cMRI in an epicardial and/or midwall myocardial pattern after normalization.

We compared the clinical characteristics and the primary and secondary endpoints in patients who received cyclophosphamide ("CYC" group) versus those who did not receive CYC ("no CYC" group) and in patients with inaugural myocarditis ("LM first" group) versus those in whom myocarditis occurred in the setting of previously diagnosed SLE ("SLE first" group).

**Statistical analysis.** Statistical analyses were conducted with GraphPad software version 6.0. Quantitative variables were described as the median and interquartile range, and qualitative variables were described as percentages. Comparisons between groups were made with Fisher's exact test for qualitative variables and Mann-Whitney U test for quantitative variables. Comparison of LVEF at last visit versus baseline was performed with Wilcoxon matched-pairs signed-rank test. All of the tests were 2-sided, and  $p$  values  $< 0.05$  were considered statistically significant.

## RESULTS

**Patient selection.** Our initial data search identified 74 patients. Forty patients were excluded because of the absence of definite diagnosis of SLE ( $n = 32$ ), lack of data ( $n = 3$ ), final diagnosis of Takotsubo cardiomyopathy ( $n = 1$ ), left ventricular dysfunction due to septic shock ( $n = 3$ ), or catastrophic antiphospholipid syndrome ( $n = 1$ ). Five cases

were common between the 2 units. Thus, the final analysis included 29 patients.

**Demographic and clinical characteristics.** The demographic characteristics are presented in Table 1. Patients were European in 55.2% of cases. The sex ratio (M/W) was 1/8.6. The median age at the time of myocarditis diagnosis was 30 years (range 16–57). The median SLE Disease Activity Index (SLEDAI) score was 8 (range 4–21) at baseline. Eleven patients exhibited concomitant renal failure (defined by a decline in glomerular filtration rate < 60 mm/min) or proteinuria (> 0.5 g/24 h), and 8 underwent renal biopsy (class IV lupus nephritis, n = 5; class IV + V lupus nephritis, n = 1; class III lupus nephritis, n = 2). The median blood creatine level was 75 µl/l (range 45–508).

Myocarditis was the first manifestation of SLE in 17/29 cases (58.6%). Among the patients who had been diagnosed

Table 1. Demographic and clinical characteristics of the 29 patients. Data are n (%) unless otherwise indicated.

Characteristics	
Age at diagnosis of SLE, yrs, median (range)	30 (16–57)
Sex ratio, M/F	1/8.6
Ethnicity	
White	16 (55.2)
Black	8 (27.6)
Asian	5 (17.2)
Inaugural LM	17/29 (58.6)
SLEDAI (LM) median (range)	8 (4–21)
APS	5/12
SLE before LM	12/29
Median followup SLE-LM, mos (range)	120 (2–276)
Treatments when myocarditis occurred (among the 12 patients with previously diagnosed SLE*)	
Hydroxychloroquine	5/11
Prednisone	5/11
Mycophenolate mofetil	1/11
Azathioprine	2/11
Methotrexate	1/11
No treatment	5/11
Hemodialysis	1/12
Symptoms	n** (%)
Dyspnea	20/27 (74)
Fever	17/27 (63)
Chest pain	11/27 (41)
Orthopnea	10/27 (37)
Palpitations	4/27 (15)
Signs	
Lung rales	15/27 (55)
Lower limb edema	6/27 (22)
New cardiac murmur	5/27 (18)
Jugular venous distention	3/27 (11)
Hepatomegaly	3/27 (11)
Liver pain <sup>†</sup>	2/27 (7)

\* Missing data, n = 1. \*\* Missing data, n = 2. <sup>†</sup> Right upper abdominal pain referring to right cardiac failure. LM: lupus myocarditis; APS: antiphospholipid syndrome; SLE: systemic lupus erythematosus; SLE-LM: median time between diagnosis of SLE and diagnosis of LM; SLEDAI: SLE Disease Activity Index.

with SLE prior to the onset of myocarditis (n = 12), the median time between SLE diagnosis and myocarditis was 8.5 years (2–276 mos). At baseline, 5/11 (45%) of the patients known to have SLE were undergoing no specific treatment for the disease. Five out of 11 patients (45%) were treated with hydroxychloroquine (HCQ), and 5/11 (45%) were treated with prednisone at a median dosage of 20 mg/d. Patients with previous diagnosis of SLE were not phenotypically different regardless of treatment status.

Clinical symptoms and signs are presented in Table 1. Dyspnea and thoracic pain were identified in 20/27 and 11/27 cases, respectively.

**Laboratory data.** Results of laboratory testing at the time of myocarditis diagnosis are presented in Table 2. Among the 29 patients, all tested positive for antinuclear antibodies, 24/27 (89%) tested positive for anti-dsDNA antibodies, and 10 (36%) tested positive for SSA antibodies. C3 and C4 complement were decreased in 18/25 and 17/23 cases, respectively. Troponin levels were increased in 20/25 patients (80%).

**Imaging data.** The results of imaging investigations are presented in Table 3. The most frequent abnormalities on 12 lead-electrocardiogram (available for 28 patients) were sinus tachycardia (n = 19, 68%) and nonspecific ST-T wave changes (n = 12, 43%). On chest radiography, pleural effusion was observed in 10/22 patients (45%).

All patients underwent initial echocardiography. The most common findings on presentation were pericardial effusion (n = 20, 69%), global wall motion abnormalities (n = 19, 65%), and reduced LVEF ≤ 45% (n = 19, 65%). The median LVEF at baseline was 37% (range 5–60).

Thirteen patients underwent cMRI with intravenous (IV)

Table 2. Biological characteristics at the onset of LM.

Characteristics	n	%
ANA	28/28	100
SSA antibodies	10/28	36
SSB	3/28	11
Sm	9/28	32
RNP	9/28	32
Anti-dsDNA (Farr/ELISA)	24/27	89
C3 < 0.70 g/l	18/25	72
C4 < 0.14 g/l	17/23	74
CH50 < 70%	13/18	72
Anticardiolipin	13/25	52
Anti-B2GP1	5/25	20
Lupus anticoagulant	3/23	13
Anemia (Hb < 10 g/dl)	21/27	78
Thrombocytopenia (platelet < 150 g/l)	9/28	32
Leukopenia (WBC < 4.5 g/l)	11/26	42
Troponin > 0.05 µg/l*	20/25	80
CRP > 5 mg/l	15/17	88

\* One patient underwent hemofiltration. ANA: antinuclear antibody; CRP: C-reactive protein; Hb: hemoglobin; WBC: white blood cell; LM: lupus myocarditis.

Table 3. Results of cardiac explorations at baseline and during followup. Data are n (%) unless otherwise indicated.

	LM Onset	1 Month	Last Visit
Electrocardiography	n = 28	n = 20	n = 17
Normal	3 (11)	17 (85)	16 (94)
Sinus tachycardia	19 (68)	0	0
Atrioventricular block	1 (4)	0	0
Right bundle branch block	4 (14)	3 (15)	1 (6)
ST-T wave changes	12 (43)	1 (5)	0
Q wave	2 (7)	0	0
Chest radiograph	n = 22		
Normal	3 (14)		
Cardiomegaly	4 (18)		
Pleural effusion	10 (45)		
Pulmonary infiltrates	13 (59)		
Echocardiography	n = 29	n = 23	n = 20
Normal	1 (3)	4 (17)	15 (75)
LVEF ≤ 45%	19 (66)	8 (35)	0
LVEF ≥ 55%	6 (21)	10 (43)	16 (80)
Global wall motion abnormality	19 (65)	6 (26)	2 (10)
Regional wall motion abnormality	6 (21)	6 (26)	1 (5)
Valvular dysfunction	12 (41)	6 (26)	3 (15)
Pericardial effusion	20 (69)	4 (17)	0
Median LVEF	37%	47%	60%
Cardiac MRI	13		11
Normal	0		4 (36)
LVEF ≤ 45%	7 (54)		1 (9)
Late gadolinium enhancement	9 (69)		3 (27)
Pericardial effusion	9 (69)		0

LM: lupus myocarditis; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging.

gadolinium injection. None of these patients had a normal examination. Nine patients (69%) exhibited a late gadolinium enhancement with epicardial and/or midwall pattern. Pericardial effusion was observed in 9 patients (69%). Supplementary Figure 1 (available from the authors on request) depicts high-intensity left ventricular epicardial

enhancement, corresponding to tissue edema, and T1-weighted imaging, revealing late left ventricular epicardial and midwall enhancement.

Coronary catheterization and angiography were performed in 7 patients at the onset of myocarditis. No stenosis or thrombus was observed.

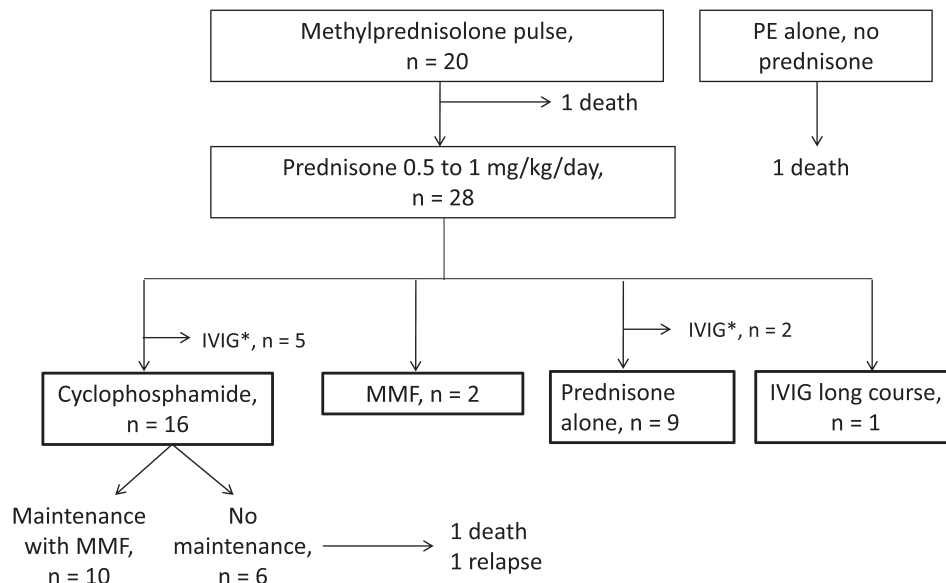


Figure 1. Treatments received during followup. \*IVIG short course. MMF: mycophenolate mofetil; IVIG: intravenous immunoglobulin; PE: plasma exchange.

Endomyocardial biopsy was performed in 3 patients. Two of those patients experienced biopsy-related complications, including cardiac tamponade and humeral artery aneurysm. One of the 3 biopsies yielded insufficient cardiac tissue for histological study. Histological analysis revealed interstitial edema and cellular inflammatory infiltration consistent with myocarditis in 1 patient. The other patient exhibited normal cardiac tissue without infiltration. Of note, in 1 case, herpes virus simplex PCR was positive in the tissue but without any cytotoxic pathogen effects.

**Initial management.** Twenty-five patients (86%) were admitted to the ICU at the onset of myocarditis. Among those patients, 11 required vasopressors and/or inotropic support (epinephrine, norepinephrine, and/or dobutamine), 4 required continuous veno-veno hemofiltration, and 3 required veno-arterial extracorporeal membrane oxygenation (ECMO) support for refractory cardiovascular dysfunction. The mean length of stay at the hospital was 42.8 days (range 8–227). Two patients died during the ICU stay as a direct consequence of myocarditis despite ECMO (Figure 1).

**Steroids and immunosuppressive treatment.** Treatments are presented in Table 4 and Figure 1. Twenty patients (69%) received IV high-dose methylprednisolone (500–1000

mg/pulse for 1 to 3 days), and all but 1 patient, who died before oral treatment, was started with 0.5 to 1 mg/kg/d prednisone (Figure 1). Sixteen patients (55%) received monthly IV CYC (500 mg to 1300 mg per pulse) for 2 to 10 months. Among those who received IV CYC, 10 (62%) received maintenance therapy with mycophenolate mofetil (MMF; 2 g/d) after CYC.

Eight patients (28%) received IV immunoglobulin (IVIG). Seven received a single perfusion (2 g/kg delivered in 3 to 5 days). One patient underwent repeated perfusions (monthly for 6 months). Four patients underwent plasma exchanges (PE).

**Followup.** Followup results are presented in Table 4 and Figure 1. The median duration of followup among the 27 patients who were alive after the first hospitalization for myocarditis was 37 months (range 4–115). All the patients normalized their troponin levels at last visit.

Among the 23 patients with echocardiography performed at 1 month, the median LVEF was 50% (range 15%–60%), and 10 (43%) achieved the primary endpoint (LVEF  $\geq$  55 % at 1 month).

One patient out of 26 (4%) relapsed during followup. The relapse occurred 2 months after the end of CYC treatment (palpitations and high troponin level without abnormal LVEF, evaluated by echocardiography); there was quick improvement with methylprednisolone pulses.

Treatments were obtained for 25 patients at last visit. Results are presented in Table 4. Among these patients, 19/25 (76%) were taking continued treatment for steroids (17/25 had  $\leq$  10 mg/d), and 9 were being treated with an immunosuppressive drug (MMF; 36%).

On the last echocardiography, 21/26 patients (excluding the 3 patients who died during initial management or followup) exhibited LVEF  $\geq$  55% (81%). The median LVEF on last echocardiography was 60% (range 50%–65%).

The final LVEF was significantly improved compared with the baseline LVEF ( $p < 0.0001$ , Figure 2).

Eleven patients underwent cMRI at the time of their last visit, and the MRI was normal for 4 patients (36%). In 3 patients, mild late gadolinium enhancement persisted because of irreversible myocardial injury (fibrosis). Among these 3 patients, 1 had normal LVEF. Four patients exhibited a persistent altered ( $< 55\%$ ) LVEF in cMRI, without gadolinium enhancement. Only 1 patient had an LVEF  $\leq$  45%. Representative images of cMRI are available from the authors on request.

Global mortality was 10.3%. Two patients died during their ICU stay as a direct consequence of myocarditis despite ECMO. Of note, the third patient who was initially assisted with ECMO improved and had a partial recovery with final LVEF at 50%. One patient died 4 years later from an unknown cause. This patient exhibited persistent alteration of LVEF  $\leq$  45% at the visit preceding the death.

**CYC vs no CYC.** We compared patients who received CYC for LM ( $n = 16$ ) and those who did not ( $n = 13$ ; Figure 2).

Table 4. Treatments and outcomes.

	n	%
Immunosuppressive regimen		
Methylprednisolone pulse	20/29	69
Prednisone, 0.5 to 1 mg/kg/d	28/29	96
CYC	16/29	55
IVIG	8/29	28
Plasma exchanges	4/29	14
MMF (first-line)	2/29	7
MMF (maintenance)	10/29	34
Outcome		
Median length of stay at hospital, days (range)	42.8 (8–227)	
Median followup, mos (range)	37 (4–115)	
Conventional unit only	4	
ICU	25	
Death due to LM	2	
Total deaths	3	
Relapse	1	
Treatment at last visit*		
Beta blockers	5/25	20
ACE inhibitors	8/25	32
HCQ	22/25	88
Prednisone $\leq$ 10 mg/d	17/25	68
Prednisone $>$ 10 mg/d	2/25	8
MMF	7/25	28
AZA	1/25	4
MTX	1/25	4

\* N = 25 (3 dead, 1 lost to followup). CYC: cyclophosphamide; IVIG: intravenous immunoglobulins; ICU: intensive care unit; LM: lupus myocarditis; ACE inhibitors: angiotensin-converting enzyme inhibitors; HCQ: hydroxychloroquine; MMF: mycophenolate mofetil; AZA: azathioprine; MTX: methotrexate.

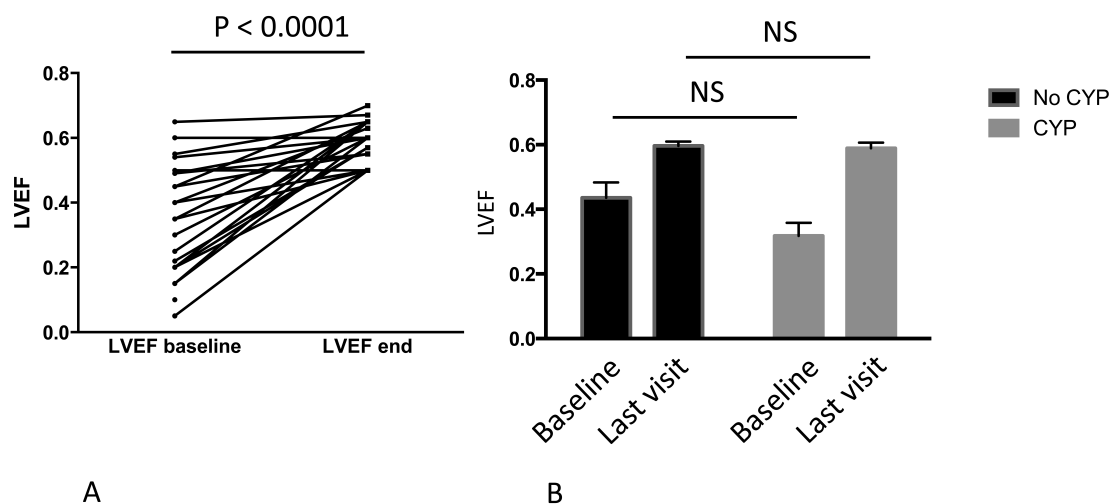


Figure 2. A. Evolution of LVEF in all patients. B. Evolution of LVEF in patients who received cyclophosphamide (CYP; n = 16) and in those who did not (no CYP; n = 13) for lupus myocarditis treatment. LVEF: left ventricular ejection function; NS: not statistically significantly different.

The initial median SLEDAI score was higher in the CYC group than in the no CYC group (13.2 vs 7.5, respectively,  $p = 0.0047$ ). Among the patients who received CYC, 9 exhibited severe involvement of at least 1 additional extra-cardiac organ (56%). There was no statistically significant difference between the 2 groups regarding ICU stay ( $p = 1.0$ ), length of hospital stay ( $p = 0.43$ ), and median LVEF at the onset ( $p = 0.06$ ), at 1 month ( $p = 0.54$ ), and at last visit ( $p = 0.91$ ). However, the median initial LVEF tended to be lower in patients treated by CYC, although this difference was not statistically significant (respectively, 0.32 vs 0.4,  $p = 0.06$ ).

**Inaugural versus noninaugural myocarditis.** We compared patients who had inaugural myocarditis (“LM first” group, n = 17) with patients in whom myocarditis occurred in the setting of previously diagnosed SLE (“SLE first” group, n = 12). There was no statistically significant difference between the 2 groups regarding demographic or clinical characteristics except for the median age at SLE diagnosis, which was lower in the “SLE first” group (23.5 yrs vs 30.0 yrs,  $p = 0.02$ ). The median age at the time of myocarditis diagnosis did not differ between the 2 groups. There was no difference between the 2 groups regarding LVEF at baseline, at 1 month, or at the end of followup, nor were there any differences in the treatments.

## DISCUSSION

We report here a series of 29 patients with SLE who were harboring myocarditis. Few short series of LM have been reported previously and have involved various inclusion criteria<sup>6,7,13,14,15</sup>. We found that SLE-related myocarditis is a life-threatening condition, particularly during the acute phase, with an overall mortality of 10.3% after a median followup of 37 months. However, cardiac recovery among survivors is frequent, with a high percentage of patients who exhibited a normal LVEF at the end of followup.

In our study, myocarditis was the first manifestation of SLE in almost 60% of the patients. This finding is consistent with previous series that reported inaugural myocarditis in 60%-88% of patients<sup>6,14,15</sup>. Among the patients already diagnosed with SLE, the median time between SLE onset and myocarditis was 8.5 years (2-276 mos). Zawadowski, *et al* reported a series of 24 patients with LM with a mean duration of SLE before myocarditis of 6.3 years<sup>6</sup>. Myocarditis can occur at any time during SLE evolution. In our study, LM could have been promoted by the lack of specific treatment in patients who were previously diagnosed with SLE; 45% of the patients with a previous diagnosis of SLE were not under any treatment when myocarditis was diagnosed, including HCQ, which is known to prevent flares<sup>16</sup>. The role of HCQ in preventing the development of myocarditis during SLE has also been reported in a multivariable logistic regression model<sup>13</sup>.

The prevalence of autoantibodies in our cohort was similar to the frequency in the general SLE population for anti-nuclear, anti-dsDNA, SSB, and SSA antibodies<sup>17</sup>. Unlike Zawadowski, *et al*, we did not observe a higher prevalence of SSA in our LM series (36% in our study; 69% in Zawadowski<sup>6</sup>).

The diagnosis of LM is difficult and features a wide range of unspecific symptoms and signs at onset<sup>15,18</sup>. According to other LM series, most of our patients (80%) exhibited high troponin levels<sup>6</sup>. High troponin levels are observed in some but not all patients with myocarditis. Smith, *et al* detected elevation of troponin I in 34% of patients with imaging evidence of myocarditis. Elevation of troponin I in myocarditis is significantly correlated with recent ( $\leq 1$  month) onset of heart failure symptoms<sup>19</sup>, suggesting that the majority of myocardial necrosis occurs early in the course of the disease. Our results could be explained by the relatively

early diagnosis of LM with more acute illness presentation than chronic heart failure disease. The recently developed high-sensitivity (hs) cardiac troponin assays may improve the sensitivity of the myocarditis diagnosis in SLE.

Pleural and pericardial effusions were noted in a relatively large number of patients. This could be because the myocarditis occurs during SLE mainly in the setting of myopericarditis.

Echocardiography was the most common imaging tool for the diagnosis of cardiac failure in our study. All patients underwent echocardiography at the onset of LM. The median LVEF was 37%, and the LVEF was < 20% in 8 cases, suggesting the potential severity of the disease.

In our series, only 3 patients underwent EMB, which is considered the gold standard to assess myocarditis diagnosis<sup>9,10</sup>, although the diagnostic criteria of myocarditis remain a matter of debate<sup>20</sup>. Myocarditis is histologically defined by the Dallas histopathologic criteria<sup>21</sup>. EMB is an invasive procedure with a high risk of complications and a low predictive negative value<sup>22</sup>. However, recent data suggest that the procedure can be safe when performed by experienced teams, with a < 1% risk of complications<sup>23</sup>. The American Heart Association/American College of Cardiology and the European Society of Cardiology have established recommendations and suggest that EMB should be performed in the setting of unexplained, new-onset heart failure of < 2 weeks' duration associated with a normal-sized or dilated left ventricle in addition to hemodynamic compromise (Class of Recommendation I, Level of Evidence B)<sup>8</sup>. In our study, EMB yielded poor information. We suggest that EMB may not be performed when myocarditis occurs in a patient with established or probable SLE, except if a differential diagnosis of viral myocarditis is suspected or in the case of a life-threatening condition. However, newly available tools, including immunohistochemistry and viral genome analysis, could prompt a more systematic EMB for myocarditis diagnosis and safe (when viral-negative) immunosuppression.

An alternative to EMB in the diagnosis of myocarditis is cMRI, which has been shown to detect myocarditis with a high degree of diagnostic accuracy<sup>24</sup>. Indeed, a combined cMRI approach using T2-weighted imaging and early and late gadolinium enhancement provides high diagnostic accuracy and is a useful tool in the diagnosis and assessment of patients with suspected acute myocarditis<sup>25</sup>. It is a safe procedure that can provide tissue characterization, localize inflammatory infiltration, and usually distinguish inflammatory lesions from ischemic lesions<sup>26</sup>. However, data regarding the performance of cMRI to guide EMB remain under debate<sup>23,24</sup>. Further, other studies are needed to establish cMRI performance in monitoring and evaluating the treatment response in myocarditis, especially in LM<sup>27</sup>.

Current treatment strategies are based on clinical experience rather than randomized trials, likely because of

the rarity of this manifestation during the course of SLE. In our study, the first-line therapy was high-dose IV methylprednisolone (69%), followed by 0.5 mg/kg/d to 1 mg/kg/d IV or oral prednisone. Steroid use seems to be prescribed by most specialists, but the duration, doses, pulses, and rhythm of tapering are not well established<sup>5,15</sup>. Immunosuppressive drugs (CYC, MMF, azathioprine, and cyclosporine) have also been used in LM. However, there are few data in the literature regarding the optimal immunosuppressive regimen in the treatment of LM. In our study, 55% of patients received CYC, but in 56% of these cases, there was at least one other case of severe organ involvement concomitant with LM that may have justified the use of this drug. Baseline LVEF tended to be lower in patients who received CYC versus those who did not, although there was no statistically significant difference. Final LVEF did not differ between CYC and no CYC groups. Additionally, patients who received CYC also received IVIG and/or PE. We conclude that CYC, which has been reported as a causal agent of myocarditis, is safe for treating LM. We also suggest that CYC could be reserved for patients with more severe disease, i.e., those with lower LVEF.

Anecdotal reports suggest that IVIG may be useful as induction-remission treatment of LM<sup>28,29,30</sup>. Rituximab has also been successfully used in a pediatric case of LM<sup>31</sup>. Congestive heart failure in those patients is treated in the supportive manner, including beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and digoxin<sup>32</sup>. For 3 of our patients, ECMO support was needed for refractory cardiovascular dysfunction, with unfortunately poor outcomes (death) for 2 of them.

The longterm outcomes of LM have rarely been reported in the literature. The median followup in our study was 37 months (range 4-115). The median LVEF was 37% at baseline, 47% at 1 month, and 60% at last visit. Moreover, although 86% of patients were admitted to the ICU at the onset of LM, the LVEF was  $\geq$  50% in all patients at the end of followup. This finding could reflect good cardiac prognosis of LM. Mechanical circulatory support was beneficial for 1 patient, as previously reported<sup>33</sup>. These results suggest that LM is severe at the beginning and that cardiac recovery remains good. The mortality rate due to LM was 7%, consistent with a previous study reporting a mortality rate of 4.2%<sup>6</sup>. For 3 patients, late gadolinium enhancement persisted, likely corresponding to fibrotic lesions. Relapse occurred in 1 patient who reported a lack of treatment adherence.

We observed in our study that LVEF recovery was good, even in patients not treated with CYC. This drug is currently used for lupus nephritis as well as for central nervous system or myocardial damage in the setting of SLE. However, recent papers have suggested that MMF may be as efficacious as CYC for remission-induction of lupus nephritis<sup>34</sup>. Moreover, CYC may exhibit several serious side effects, in particular ovarian toxicity. Our data suggest that CYC administration

should not be a standard of care in the setting of LM, especially in patients with preserved LVEF (> 40%), although these data should be confirmed.

Our study has several limitations. The study was a retrospective case series, with potential bias especially concerning treatment efficacy. Only 3 patients underwent EMB. The myocarditis diagnosis criteria included at least 2 of the following: high troponin level, cMRI abnormalities, and evidence of recent echocardiographic LVEF dysfunction. These criteria may have selected the more serious cases of LM. We cannot exclude the possibility that some patients with SLE may have less severe myocardial involvement with isolated elevated troponin without low LVEF or cMRI abnormalities. Further, in our retrospective study, only 13 patients underwent cMRI and not all the patients had T2 short-tau inversion recovery, and early and late gadolinium images<sup>25</sup>. Finally, treatment regimens were not standardized, and thus conclusions on their efficacy cannot be drawn.

LM is a rare condition that may be life-threatening at the acute phase. The major finding of our study is the good prognosis, as demonstrated by last visit LVEF ( $\geq 50\%$  in all patients). The prognosis did not differ between patients who received CYC and those who did not, although we suspect that patients with more severe disease had been treated with CYC, in addition to IVIG and PE. Although stringent criteria were applied in our study to obtain a homogeneous population, SLE-related myocarditis may present with less serious presentations, perhaps recognized with hs-troponin assays. Prospective studies are warranted to determine whether cMRI could be helpful for EBM guiding, prognosis assessment, or response monitoring. Although severe at the onset of the disease, LM usually exhibits good longterm outcomes under specific treatment, especially regarding cardiac recovery. Finally, treatment regimens were not standardized and thus conclusions about their efficacy cannot be drawn.

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