

## Research Article

# Efficacy and Tolerance of TNF alpha Inhibitor Treatment in Cardiac Sarcoidosis

Deborah Puyraimond-Zemmour<sup>1,4</sup>, Catherine Chapelon-Abric<sup>1,4</sup>, Diane Bouvry<sup>5</sup>, Marc Ruivard<sup>6</sup>, Marc André<sup>7</sup>, Laurent Pé-rard<sup>8</sup>, David Saadoun<sup>1,2,3,4</sup>, Pascal Seve<sup>9</sup>, Patrice Cacoub<sup>1,2,3,4,\*</sup>

<sup>1</sup>Sorbonne Universités, UPMC Univ Paris 06, UMR 7211, and Inflammation-Immunopathology-Biotherapy Department (DHU i2B), F-75005, Paris, France

<sup>2</sup>INSERM, UMR-S 959, F-75013, Paris, France

<sup>3</sup>CNRS, FRE3632, F-75005, Paris, France

<sup>4</sup>AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Department of Internal Medicine and Clinical Immunology, Centre de Référence des Maladies Autoimmunes et Systémiques Rares, F-75013, Paris, France

<sup>5</sup>Hopital Avicenne, Department of Pneumology, Bobigny, France

<sup>6</sup>CHU Estaing, Department of Internal Medicine, Clermont-Ferrand, France

<sup>7</sup>CHU Montpied, Department of Internal Medicine, Clermont-Ferrand, France

<sup>8</sup>Department of Internal Medicine, Hopital Saint Joseph-Saint Luc, Lyon, France

<sup>9</sup>Department of Internal Medicine, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, University of Lyon I, F-69004, Lyon, France

\*Corresponding author: Patrice Cacoub, Département de Médecine Interne et d'Immunologie Clinique, Hôpital Pitié-Salpêtrière, 47-83, Boulevard de l'Hôpital, 75013, Paris, France ; Tel : +33142178027 ; Fax : +33142178033 ; Email: patrice.cacoub@aphp.fr

**Citation:** Puyraimond-Zemmour D, Chapelon-Abric C, Bouvry D, Ruivard M, André M, et al. (2018) Efficacy and Tolerance of TNF alpha Inhibitor Treatment in Cardiac Sarcoidosis. Int J Exp Clin Res: IJEACR-121. DOI: 10.29011/IJEACR-121.000021

**Received Date:** 05 March, 2018; **Accepted Date:** 24 March, 2018; **Published Date:** 30 March, 2018

## Abstract

**Background:** Cardiac Sarcoidosis (CS) accounts for 85% of sarcoidosis-related deaths in Japan and 13-25% in North America.

**Objective:** To evaluate effectiveness and tolerance of TNF alpha inhibitor (TNFI) treatment in CS.

**Methods:** From a French multicenter cohort of patients with extra-thoracic sarcoidosis, we retrospectively analyzed patients who fulfilled following inclusion criteria:

- A definite histologically proven extra-thoracic sarcoidosis
- A diagnosis of CS based on the 2011-Heart Rhythm Society consensus, and
- who received a TNFI. The response to TNFI treatment was analyzed on cardiac clinical symptoms/signs and cardiac imaging abnormalities. Complete responders showed a complete normalization of all baseline abnormal exams.

**Results:** Among 19 patients, baseline characteristics included chest pain/heart failure (42%) and abnormal findings on cardiac MRI (73%), EKG (72%), echocardiography (59%), thallium scintigraphy (69%) and 18 FDG PET scan (44%). CS was refractory to corticosteroids plus immunosuppressant i.e. methotrexate (n=14/19), cyclophosphamide (n=10/19), azathioprine (n=7/19), and mycophenolate mofetyl (n=3/19). After a mean follow up of 36.6 months, 26.3% of patients were complete responders and 47.4% partial responders. The mean daily dose of corticosteroids was 21.4 mg at baseline versus 10.9 mg at the last visit (p<0.001). Four patients had to withdraw TNFI because of infection. Three patients died (lung cancer, infection-related respiratory failure, cardiac failure).

**Conclusion:** TNF alpha inhibitor treatment led to a complete/partial cardiac response in 74% of patients with a cardiac sarcoidosis refractory to immunosuppressant, with a steroid sparing-effect. Adverse infectious events led to TNF alpha inhibitor withdrawal in 21% of patients.

**Key Messages**

- TNF inhibitor appears to be an effective treatment with a complete/partial response in 74% of patients with a cardiac sarcoidosis refractory to immunosuppressant.
- TNFI inhibitor should be used with cautious in patients with a cardiac sarcoidosis refractory to corticosteroid and immunosuppressive therapy. There is a risk of side effects: infection (21.1%) and chest pain (10.5%).
- TNF inhibitor allows a significant corticosteroid-sparing effect in patients with a cardiac sarcoidosis refractory to immunosuppressant.

**Keywords:** Cardiac sarcoidosis; Immunosuppressive drugs; Infliximab; TNF alpha inhibitor

**Introduction**

Sarcoidosis is a multi-system inflammatory disorder of unknown etiology resulting in formation of non-caseating granulomas. In patients with sarcoidosis, a cardiac involvement has been reported in 3 to 40% of cases in clinical series according to diagnostic criteria and procedures [1-4], and in up to 30% of cases in pathology series [5,6]. Cardiac Sarcoidosis (CS) is a potentially life threatening condition as it is reported to account for 13 to 25% of sarcoidosis-related deaths in North America and up to 85% in Japan [7,8]. Main clinical manifestations reported in CS include conduction abnormalities, ventricular arrhythmias, congestive heart failure, and sudden death [9-11]. There is no controlled clinical trial to define the best strategy of CS treatment. Usually, corticosteroid therapy is given at 0.5 to 1.0 mg/kg/day for a prolonged duration [12-13]. Other immunosuppressive therapies have been used including methotrexate, azathioprine, cyclophosphamide and mycophenolate mofetyl [14]. The Place of TNF Alfa Inhibitor (TNFI) in the treatment of idiopathic chronic heart failure is debated. On one hand, the use of high doses of TNFI has been reported to adversely affect the clinical condition of patients with moderate-to-severe chronic heart failure [15,16]. On the other hand, case series and small cohorts have reported efficacy of infliximab and adalimumab in patients with chronic heart failure, although these drugs are not considered as current standard therapy [17-20]. There is a lack of data about the efficacy of TNFI in CS. The objective of this study was to evaluate effectiveness and tolerance of TNFI in the treatment of CS.

**Methods**

From a large French multicenter cohort of 132 patients with extra-thoracic sarcoidosis (cohort STAT, Sarcoidose Traitée par Anti-TNF alpha) [21], we retrospectively analyzed patients who

fulfilled following inclusion criteria 1) a definite histologically proven extra-thoracic sarcoidosis, 2) a diagnosis of CS based on the 2011-Heart Rhythm Society consensus [22] (Online supplementary Table 1, Table 2), and 3) who received at least one course of TNFI. Other data collected at diagnosis and during the follow-up included main extra-cardiac sarcoidosis manifestations and treatments. No patient had comorbid conditions known to induce cardiac disease or pulmonary hypertension. For all patients, following cardiac diseases have been excluded: ischemic, valvular and alcohol cardiomyopathy, as well as Lyme disease, amyloidosis, dermato-polymyositis, granulomatosis with polyangiitis, Takayasu arteritis, rheumatoid arthritis and myocarditis.

<b>1.</b>	<b>Histological diagnosis of cardiac sarcoidosis</b>
	Endomyocardial biopsy specimens with non-caseating epithelioid granulomas and no alternative cause identified
<b>2.</b>	<b>Clinical diagnosis of probable cardiac sarcoidosis</b>
	Histologic diagnosis of extracardiac sarcoidosis and none or more of the following is present while reasonable alternative cardiac causes other than CS have been excluded:
	<ul style="list-style-type: none"> <li>• Corticosteroid or immunosuppressive therapy responsive cardiomyopathy or hearth block                             <ul style="list-style-type: none"> <li>• Unexplained reduced LVEF (&lt;40%)</li> </ul> </li> <li>• Mobitz type two second degree heart block or third degree heart block                             <ul style="list-style-type: none"> <li>• Depressed left ventricular ejection fraction &lt; 50 %</li> </ul> </li> <li>• Patchy uptake on cardiac FDG-TEP in a pattern consistent with CS</li> <li>• Late gadolinium enhancement on cardiac magnetic resonance imaging in a pattern consistent with CS</li> <li>• Positive gadolinium uptake in a pattern consistent with CS</li> </ul>

<p>« Probable Cardiac Sarcoidosis » defined as &gt; 50% likelihood</p> <p>LVEF: left ventricular ejection fraction</p> <p>FDG-TEP: fluorodeoxyglucose positron emission tomography</p> <p>CS: cardiac sarcoidosis</p>
---

**Online supplementary Table 1:** Summary of Heart Rhythm Society consensus statement of cardiac sarcoidosis.

Patient	Extra-cardiac sarcoidosis involvement	Resistant or intolerant to immunosuppressive therapy
1	Pulmonary, renal, pleural	Methotrexate
2	Pulmonary, eyes, CNS, peripheral nerve, liver	Methotrexate, cyclophosphamide
3	Pulmonary, eyes, CNS, liver, salivary gland	Cyclophosphamide
4	Pulmonary, liver, osteo-arthritis	Methotrexate, cyclophosphamide, azathioprine, MMF
5	Pulmonary, peripheral nerve, liver, spleen, lymph nodes, salivary gland, ENT, orchitis	Methotrexate, cyclophosphamide, azathioprine
6	CNS	Methotrexate, azathioprine
7	Skin, spleen	-
8	CNS	Cyclophosphamide
9	CNS	Methotrexate, cyclophosphamide
10	Pulmonary	Methotrexate, cyclophosphamide
11	CNS	Cyclophosphamide
12	-	Methotrexate, cyclophosphamide
13	Pulmonary, skin	Methotrexate, azathioprine
14	Pulmonary, skin, liver, ENT	Methotrexate
15	Pulmonary, skin, CNS, liver, ENT, osteo-arthritis	Methotrexate, azathioprine
16	Pulmonary, skin	Methotrexate, azathioprine

17	Pulmonary, skin, neurological peripheral, spleen, ENT, osteo-arthritis	Methotrexate, azathioprine, MMF
18	Pulmonary, skin, eyes, lymph nodes, ENT, osteo-arthritis	Methotrexate, MMF
19	Pulmonary	Cyclophosphamide
CNS, central nervous system; ENT, ears-nose-throat; MMF, mycophenolate mofetyl.		

**Online supplementary Table 2:** Main features of sarcoidosis and type of immunosuppressive therapy at baseline.

### Anti-TNF Alpha Treatment

After starting TNFI, patients have been evaluated every  $3 \pm 0.5$  months for 6 months, at 12 months, at the end of TNFI, and at the last visit. The response to TNFI treatment was analyzed on multiple criteria including (i) cardiac clinical symptoms/signs i.e. New York Heart Association (NYHA) class for dyspnea, presence versus absence of signs of heart failure (right, left or both), and presence vs. absence of cardiac rhythm or conduction disturbances (auricular, ventricular or both), and (ii) presence versus absence of cardiac imaging abnormalities on echography, thallium scintigraphy, MRI, or 18 FDG PET scan. Patients were classified as complete responders when they showed a complete normalization of all abnormal exams at baseline (clinical and imaging). Non responders were defined by the absence of improvement of all abnormal baseline exams or an aggravation on at least one exam. All other cases were defined as partial responders. For complete/partial responders, we analyzed at baseline and at the end of follow up/end of TNFI the daily dose of corticosteroids and other immunosuppressant received.

The tolerance of TNFI treatment was analyzed for infections (tuberculosis, fungal infection, hepatitis B virus reactivation...), episodes of hypersensitivity or allergy, demyelinating lesions (multiple sclerosis), autoimmune diseases, malignant tumors and cytopenia with a clinical impact. The clinical impact was defined for thrombocytopenia as a major bleeding (requiring red cell transfusion or hospitalization), and for neutropenia and leucopenia as a proved episode of infection (requiring antibiotics, antivirals or hospitalization). The authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

## Results

### 1.1. Baseline Characteristics

The median age at sarcoidosis diagnosis was 39.5 years

[range 20-73], with a female/male ratio of 0.32 (Table 1). Patients were mainly Caucasian (53%), originating from Sub-Saharan Africa (16%), Caribbean (16%) and Maghrebian (5%) (Table 1). None had had cancer. Main classical cardiovascular risk factors were arterial hypertension (1 patient), type 2 diabetes mellitus (5 patients) and dyslipidaemia (1 patient) but they were not associated to ischemic heart disease. The mean body mass index was 28.9 kg/m<sup>2</sup> [range 21.7-45.1]. At baseline, 8/19 (42%) patients had chest pain and/or heart failure signs [NYHA class 3 (n=5), class 4 (n=1), class 2 (n=2) and class 1 (n=11)], and abnormal test on EKG (13/18, 72%), cardiac MRI (11/15, 73%), thallium scintigraphy (9/13, 69%), 18 FDG PET scan (4/9, 44%), and echocardiography (10/17, 59%). No patient presented CS as the first sarcoidosis manifestation. Of note, 16/19 (84%) patients had a multivisceral extra-thoracic sarcoidosis and 6/19 (32%) more than four organs (heart excluded) involved by sarcoidosis (Table 1).

Parameters	Number (%) N = 19 patients
Age at sarcoidosis diagnosis, median (yrs)	39.4 (20-73)
Sex ratio (female/male)	0.32
<b>Ethnic origin, n (%)</b>	
Caucasian	10/19 (53)
Sub Saharan Africa	3/19 (16)
Maghreb	1/19 (5)
Caribbean	3/19 (16)
Indian	1/19 (5)
Asian	1/19 (5)
<b>Extra-cardiac involvement of sarcoidosis, n (%)</b>	
Pulmonary abnormal chest X rays	13/19 (68)
Skin	6/19 (32)
CNS	7/19 (37)
Neurological, peripheral	3/19 (16)
Liver	6/19 (32)
ENT	5/19 (26)
Parotid	2/19 (11)
Eyes	3/19 (16)
Spleen	3/19 (16)
Lymph nodes	2/19 (11)

Renal	1/19 (5)
<b>Previous immunosuppressant, n (%)</b>	
Methotrexate	14/19 (74)
Cyclophosphamide	9/19 (47)
Azathioprine	7/19 (37)
Mycophenolate mofetyl	3/19 (16)
CNS, central nervous system; ENT, ears, nose, throat.	

**Table 1:** Baseline characteristics of patients with cardiac sarcoidosis. **Treatment by TNF Alpha Inhibitor, Response Rates and Tolerance**

The mean sarcoidosis duration before starting TNFI was 156.7 months [19- 420]. TNFI treatment was indicated for cardiac involvement alone [4/19 (21.1%) patients] or associated with other sarcoidosis organ involvement [i.e. neurological 6/19 (31.6%), pulmonary 6/19 (31.6%), skin 5/19 (26.3%), ocular 1/19 (5.3%) and ear-nose-throat 1/19 (5.3%)]. Most patients were resistant or intolerant to one to four previous non-steroid immunosuppressive therapy i.e. methotrexate (14/19), cyclophosphamide (10/19), azathioprine (7/19), and mycophenolate mofetyl (3/19) (Table 1). Nineteen patients received Infliximab infusion (5 mg/kg) at baseline, week 2, and then every 4 to 8 weeks based on physician in charge decision. Only one patient received firstly etanercept (25 mg twice per week) for 10 days, and received thereafter infliximab.

After a mean follow up of 36.6 months [3; 104] after starting TNFI, 5/19 (26.3%) patients were complete responders, 9/19 (47.4%) partial responders and 5/19 (26.3%) non-responders (Table 2). Two out of 19 (10.5%) patients developed a CS relapse during the TNFI treatment while they were receiving infliximab every 6 weeks. These patients returned to Infliximab infusion every 3 to 4 weeks with a complete response for one and a partial response for the other. Nine (47.4%) patients had had at least one infection (viral, fungal or bacterial). After a mean follow-up of 53.5 months [8; 111], four patients had to withdraw definitely TNFI treatment because of infection at 1 month (one patient), 8 months (two patients) and 38 months (one patient) after starting TNFI. Of these, three patients were partial responders and one non-responder. Two others had to withdraw TNFI because of pain chest and repolarization disturbance on EKG during the infusion at 10 and 16 months, with one non-responder and one partial responder. There was no episode of hypersensitivity or allergy. Three patients died, from cardiac failure (1), lung cancer (1) and respiratory failure of infectious origin (1). One patient developed a lung cancer. No case of lymphoma, auto-immune or demyelinating disease was noted.

Patient number	Visit	Heart failure or chest pain	EKG	Echo cardiography	Holter EKG	Thallium scintigraphy	Cardiac MRI	18 FDG PET scan	Response
1	Baseline	0	0	1	0	0	0	0	Partial
1	Last visit	0	0	1	0	0	0	0	
2	Baseline	0	1	0	0	0	1	ND	Complete
2	Last visit	0	0	0	0	0	0	ND	
3	Baseline	0	1	1	0	0	ND	0	Complete
3	Last visit	0	0	0	0	0	ND	0	
4	Baseline	1	1	1	0	0	0	0	Partial
4	Last visit	0	1	1	0	ND	ND	0	
5	Baseline	1	ND	1	0	ND	0	ND	No
5	Last visit	1	ND	1	ND	ND	ND	ND	
6	Baseline	0	1	1	ND	1	1	0	Partial
6	Last visit	0	1	ND	0	ND	0	0	
7	Baseline	1	1	1	ND	ND	1	1	Partial
7	Last visit	1	1	0	ND	ND	1	ND	
8	Baseline	0	1	ND	ND	1	0	ND	Partial
8	Last visit	0	1	0	0	0	0	0	
9	Baseline	0	0	0	ND	1	1	ND	No
9	Last visit*	0	1	0	ND	1	1	ND	
10	Baseline	1	0	ND	1	ND	1	ND	Complete
	Last visit	0	0	0	ND	ND	0	ND	
11	Baseline	0	0	1	ND	1	1	1	Partial
11	Last visit	0	0	ND	0	ND	0	1	
12	Baseline	1	0	0	ND	1	1	ND	Partial
12	Last visit	0	0	1	ND	1	0	ND	
13	Baseline	1	1	0	1	0	1	0	Complete
13	Last visit	0	0	0	ND	ND	0	ND	
14	Baseline	0	1	1	ND	1	ND	ND	No **
14	Last visit *	0	0	0	0	0	1	1	
15	Baseline	0	1	0	ND	ND	ND	ND	No
15	Last visit	1	1	1	1	1	1	1	
16	Baseline	1	1	0	ND	ND	1	1	No
16	Last visit	1	1	ND	ND	1	ND	ND	
17	Baseline	1	1	0	ND	1	ND	ND	Partial
17	Last visit	0	0	0	ND	ND	ND	ND	
18	Baseline	0	1	1	1	1	1	ND	Partial
18	Last visit	0	1	0	0	ND	ND	ND	
19	Baseline	1	1	1	ND	1	ND	1	Complete
19	Last visit	1	1	1	ND	ND	ND	0	

0: normal; 1: abnormal; ND: not done; EKG: electrocardiogram; TNFI: TNF inhibitor;

18 FDG PET scan: 18 fluorodeoxyglucose positron emission tomography;

LGE: Late gadolinium enhancement; LV: left ventricle; \* no TNFI; \*\* this patient received only two TNFI infusions.

**Table 2:** Main cardiac features in patients with cardiac sarcoidosis at baseline and at the end of TNFI.

All patients received corticosteroids during TNFI treatment. The mean daily dose of prednisone-equivalent was 21.4 mg [0; 60] at baseline versus 10.9 mg [0; 40] at the end of follow-up or the end of TNFI (P<0.0001) (Table 3). Forty-six percent of patients (7/15) have a cardiac treatment at the end of TNFI/end of the follow up. Before starting TNFI treatment, eighteen patients had received immunosuppressant (except corticosteroids). During TNFI treatment, most patients were receiving immunosuppressant therapy i.e. methotrexate (n=13 patients), mycophenolate mofetil (n=1), and azathioprine (n=1). Three patients had a cardiac defibrillator and one a pacemaker.

Patient number	Daily dose of corticosteroids (mg)		Immunosuppressive treatment at the end of TNFI/end of follow-up	Cardiac treatment at the end of TNFI/end of follow-up	Response to TNFI
	At baseline	At the end of TNFI/end of follow-up			
1	20	NA	NA	NA	Partial
2	30	5	TNFI, methotrexate	No	Complete
3	30	10	TNFI, methotrexate	No	Complete
4	30	13	TNFI	Yes	Partial
5	40	10	TNFI, methotrexate	Yes	No
6	7	5	TNFI, methotrexate	No	Partial
7	40	40	TNFI, azathioprine	Yes	Partial
8	10	8	TNFI, methotrexate	No	Partial
9	20	15	-	NA	No
10	15	10	TNFI, methotrexate	Yes	Complete
11	15	NA	-	NA	Partial
12	15	15	TNFI, methotrexate	No	Partial
13	15	2.5	TNFI	No	Complete
14	15	NA	Switch TNFI/Arava	NA	No
15	30	15	Switch TNFI/Methotrexate	No	No
16	0	0	TNFI, methotrexate	Yes	No
17	0	7.5	Switch TNFI/ Arava	Yes	Partial
18	15	15	Switch TNFI/ Methotrexate	No	Partial
19	60	5	TNFI	Yes	Complete

TNFI: TNF inhibitor; NA: not available

**Table 3:** Corticosteroids, immunosuppressive therapy and cardiac treatment for each patient with cardiac sarcoidosis, at baseline and at the end of TNF inhibitor (TNFI)/end of follow-up.

## Discussion

Cardiac sarcoidosis remains a life-threatening condition with major difficulties in patient's refractory to corticosteroids and immunosuppressant. In the present series of 19 patients with a definite CS refractory to corticosteroid plus immunosuppressive therapy, TNFI showed a complete/partial response in 74% of patients, with a significant corticosteroid-sparing effect. Of note, TNFI had to be withdrawn in 21% of patients because of infectious side effects. In previous reports, infliximab and adalimumab have showed a good efficacy in patients with refractory extra-cardiac sarcoidosis i.e. involvement of lungs, eyes, bone, and central nervous system [23-26].

Our results in patients with CS are in agreement with such results as well as with recommendations. Infliximab is recommended in CS when sarcoidosis activity is the only cause of heart failure [18,27,28]. We did not find new adverse events of TNFIs.

There was no cardiac function degradation after the use of TNFI in CS patients as described in patients with severe idiopathic heart failure [16]. In the present series, no case of vasculitis or exacerbation as interstitial pneumonia was noted [29]. The most frequent adverse event was infection in patients who all received previously corticosteroids and immunosuppressant [19]. One patient died from respiratory failure of infectious origin. Two other patients died, one from cardiac failure and one from a lung cancer. However, cardiac sarcoidosis is known to have a very poor prognosis, with an estimated mortality rate of up to 50% [7]. The 5-year survival rate was reported to be 60 to 90% in patients who received steroids alone or combined with immunosuppressive therapy [8,13,14]. In the present series, one patient had an initial improvement of cardiac function under TNFI, but died after 30 months of a cardiac failure. TNFI had to be stopped because of chest pain and repolarization disturbance during the infusion in one non-responder and one partial responder.

We acknowledge some limitations of the present study. The gold standard for the diagnosis of CS has long been considered to be the endomyocardial biopsy. However, this invasive method showed a lack of sensitivity due to the heterogeneous distribution of granuloma within the heart [30,31]. The retrospective nature of this study is a well-known limitation e.g. the number of missing data for imaging in the present study. Controlled randomized studies are needed to better define investigation and treatment strategies. Corticosteroid treatment was a possible bias of confusion of the efficacy of TNFI although the latter permitted a steroid-sparing effect. Finally, the small number of patients should be analyzed considering the rarity of CS. In conclusion, despite the risk of infection, TNFI appear to be an effective treatment in patients with refractory cardiac sarcoidosis. Further studies are needed to confirm these results in larger population and to identify predictors of response to TNFI in patients with cardiac sarcoidosis.

## Conflict of Interest

There is no personal or financial support or author involvement with organization with financial interest in the subject.

## References

1. Hiraga H, Iwai K, Hiroe M, Omori F, Sekiguchi M, et al. (1993) Guideline for the diagnosis of cardiac sarcoidosis: study report on diffuse pulmonary diseases Tokyo. The Japanese Ministry of Health and Welfare 23-24.
2. Chapelon-Abric C, de Zuttere D, Duhaut P, Veyssier P, Wechsler B, et al. (2004) Cardiac sarcoidosis: a retrospective study of 41 cases. *Medicine (Baltimore)* 83: 315-334.
3. Hamzeh NY, Wamboldt FS, Weinberger HD (2012) Management of cardiac sarcoidosis in the United States: a Delphi study. *Chest* 141: 154-162.
4. Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, et al. (2015) Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. *Circulation* 131: 624-632.
5. Perry A, Vuitch F (1995) Causes of death in patients with sarcoidosis. A morphologic study of 38 autopsies with clinicopathologic correlations. *Arch Pathol Lab Med* 119: 167-172.
6. Hu X, Carmona EM, Yi ES, Pellikka PA, Ryu J (2016) Causes of death in patients with chronic sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 33: 275-280.
7. Iwai K, Tachibana T, Takemura T, Matsui Y, Kitaichi M, et al. (1993) Pathological studies on sarcoidosis autopsy. I. Epidemiological features of 320 cases in Japan. *Acta Pathol Jpn* 43: 372-376.
8. Chiu CZ, Nakatani S, Zhang G, Tachibana T, Ohmori F, et al. (2005) Prevention of left ventricular remodeling by long-term corticosteroid therapy in patients with cardiac sarcoidosis. *Am J Cardiol* 95: 143-146.
9. Nery PB, Beanlands RS, Nair GM, Green M, Yang J, et al. (2014) Atrioventricular block as the initial manifestation of cardiac sarcoidosis in middle-aged adults. *J Cardiovasc Electrophysiol* 25: 875-881.
10. Kim JS, Judson MA, Donnino R, Gold M, Cooper LT Jr, Prystowsky EN et al. (2009) Cardiac sarcoidosis. *Am Heart J*. 157: 9-21.
11. Padala SK, Peaslee S, Sidhu MS, Steckman DA, Judson MA (2017) Impact of early initiation of corticosteroid therapy on cardiac function and rhythm in patients with cardiac sarcoidosis. *Int J Cardiol* 227: 565-570.
12. Nagai T, Nagano N, Sugano Y, Asaumi Y, Aiba T, et al. (2016) Effect of Discontinuation of Prednisolone Therapy on Risk of Cardiac Mortality Associated With Worsening Left Ventricular Dysfunction in Cardiac Sarcoidosis. *Am J Cardiol* 117: 966-971.
13. Yazaki Y, Isobe M, Hiroe M, Morimoto S, Hiramitsu S (2001) Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. *Am J Cardiol* 88: 1006-1010.
14. Chapelon-Abric C, Sene D, Saadoun D, Cluzel P, Vignaux O, et al. (2017) Cardiac sarcoidosis: Diagnosis, therapeutic management and prognostic factors. *Arch Cardiovasc Dis* 110: 456-465.
15. Chung ES, Packer M, Hung Lo K, Fasanmade AA, Willerson JT (2003) Randomized, Double-Blind, Placebo-Controlled, Pilot Trial of Infliximab, a Chimeric Monoclonal Antibody to Tumor Necrosis Factor- $\alpha$ , in Patients With Moderate-to-Severe Heart Failure. *Circulation* 107: 3133-3140.
16. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT. (2003) Anti-TNF Therapy Against Congestive Heart Failure Investigators. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor- $\alpha$ , in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation* 107: 3133-3140.
17. Uthman I, Touma Z, Khoury M (2007) Cardiac sarcoidosis responding to monotherapy with infliximab. *Clin Rheumatol* 26: 2001-2003.
18. Barnabe C, McMeekin J, Howarth A, Martin L (2008) Successful treatment of cardiac sarcoidosis with infliximab. *J Rheumatol* 35: 1686-1687.

19. Chapelon-Abrie C, Saadoun D, Biard L, Sene D, Resche-Rigon M, et al. (2015) Long-term outcome of infliximab in severe chronic and refractory systemic sarcoidosis: a report of 16 cases. *Clin Exp Rheumatol* 33: 509-515.
20. Jamilloux Y, Cohen-Aubart F, Chapelon-Abrie C, Maucourt-Boulch D, Marquet A, et al. (2017) Efficacy and safety of tumor necrosis factor antagonists in refractory sarcoidosis: A multicenter study of 132 patients. *Semin Arthritis Rheum* 47: 288-294.
21. Marquet A, Chapelon-Abrie C, Maucourt-Boulch D, Cohen-Aubart F, Pérard L, et al. (2017) Efficacy and safety of TNF antagonists in ocular sarcoidosis: data from the French registry STAT. *Sarcoidosis vasculitis and diffuse lung diseases* 34: 74-80.
22. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, et al. (2014) HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm* 11: 1305-1323.
23. Baughman RP, Drent M, Kavuru M, Judson MA, Costabel U, et al. (2006) Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med* 174: 795-802.
24. Judson MA, Baughman RP, Costabel U, Flavin S, Lo KH, et al. (2008) Centocor T48 Sarcoidosis Investigators. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. *Eur Respir J* 31: 1189-1196.
25. Maneiro JR, Salgado E, Gomez-Reino JJ, Carmona L (2012) Efficacy and safety of TNF antagonists in sarcoidosis: data from the Spanish registry of biologics BIOBADASER and a systematic review *Semin Arthritis Rheum* 42: 89-103.
26. Joubert B, Chapelon-Abrie C, Biard L, Saadoun D, Demeret S, et al. (2017) Association of Prognostic Factors and Immunosuppressive Treatment With Long-term Outcomes in Neurosarcoidosis. *JAMA Neurol* 74: 1336-1344.
27. Drent M, Cremers JP, Jansen TL, Baughman RP (2014) Practical eminenence and experience-based recommendations for use of TNF- $\alpha$  inhibitors in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis.* 31: 91-107.
28. Uthman I, Touma Z, Khoury M (2007) Cardiac sarcoidosis responding to monotherapy with infliximab. *Clin Rheumatol* 26: 2001-2003.
29. Ramos-Casals M, Perez-Alvarez R, Perez-de-Lis M, Xaubet A, Bosch X (2011) Pulmonary disorders induced by monoclonal antibodies in patients with rheumatologic autoimmune diseases. *Am J Med* 124: 386-394.
30. Hulten E, Aslam S, Osborne M, Abbasi S, Bittencourt MS, et al. (2016) Cardiac sarcoidosis-state of the art review. *Cardiovasc Diagn Ther* 6: 50-63.
31. Moiseyev SV, Kornev BM, Shatkovsky NP, Eventov AZ, Pisareva NA (1987) Non-invasive diagnosis of cardiac sarcoidosis. *Lancet* 2: 739-740.