Cardiac sarcoidosis: systematic review of the literature on corticosteroid and immunosuppressive therapies

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Shareable abstract (@ERSpublications)
Corticosteroids are the mainstay treatment for cardiac sarcoidosis. Conventional immunosuppressive agents might be of interest at diagnosis. Cohort studies are clearly heterogeneous. Large cohort and prospective studies using "strong" end-points are lacking. https://bit.ly/3t9Rv8O

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Abstract

Background Cardiac sarcoidosis (CS) is a life-threatening condition in which clear recommendations are lacking. We aimed to systematically review the literature on cardiac sarcoidosis treated by corticosteroids and/or immunosuppressive agents in order to update the management of CS.

Methods Using PubMed, Embase and Cochrane Library databases, we found original articles on corticosteroid and standard immunosuppressive therapies for CS that provided at least a fair Scottish Intercollegiate Guidelines Network (SIGN) overall assessment of quality and we analysed the relapse rate, major cardiac adverse events (MACEs) and adverse events. We based our methods on the PRISMA statement and checklist.

Results We retrieved 21 studies. Mean quality provided by SIGN assessment was 6.8 out of 14 (range 5–9). Corticosteroids appeared to have a positive impact on left ventricular function, atrioventricular block and ventricular arrhythmias. For corticosteroids alone, nine studies (45%, n=351) provided data on relapses, representing an incidence of 34% (n=119). Three studies (14%, n=73) provided data on MACEs (n=33), representing 45% of MACEs in patients treated by corticosteroid alone. Nine studies provided data on adjunctive immunosuppressive therapy, of which four studies (n=78) provided data on CS relapse, representing an incidence of 33% (n=26). Limitations consisted of no randomised control trial retrieved and unclear data on MACEs in patients treated by combined immunosuppressive agents and corticosteroids.

Conclusion Corticosteroids should be started early after diagnosis but the exact scheme is still unclear. Studies concerning adjunctive conventional immunosuppressive therapies are lacking and benefits of adjunctive immunosuppressive therapies are unclear. Homogenous data on CS long-term outcomes under corticosteroids, immunosuppressive therapies and other adjunctive therapies are lacking.

Introduction

Sarcoidosis is a rare multisystemic granulomatous disease of unknown aetiology, which most frequently involves the lungs, lymph nodes, skin, eyes, liver and spleen [1]. Cardiac sarcoidosis (CS) is a rare condition, with symptomatic cardiac features reported in 2.3–39% of patients with sarcoidosis [2, 3]. Cardiac involvement in sarcoidosis ranges from 27% to 50% in morphological studies [4, 5]. Although CS is rare, it can be a life-threatening condition, mainly with left ventricular (LV) systolic failure, ventricular arrhythmias (VAs) and atrioventricular (AV) conduction abnormalities, which can lead to disability or cardiac sudden death [6]. There has been a great deal of progress in research [7], diagnosis and management [8] of CS over the past few years. Corticosteroid therapy (CT) remains the mainstay treatment for CS, although there is a lack of prospective controlled studies, and treatment should be started early

after CS diagnosis [9]. The treatment is recommended on the basis of clinicians' experience, expert opinions and observational cohort studies. To our knowledge, only two studies have investigated the impact of adjunctive immunosuppressive therapy on CS [10, 11]. In 2013, Sadek *et al.* [9] published a systematic review of CT as the mainstay treatment for CS.

We conducted a systematic review of the literature on CT and/or immunosuppressive therapy (IT) for CS. The aim of this study was to evaluate the impact of CT and/or immunosuppression on CS relapse, on the effects of sparing CT and on major adverse cardiovascular events (MACEs) (defined as cardiac death, ventricular fibrillation, sustained ventricular tachycardia or hospitalisation for heart failure), as well as to study adverse drug events.

Methods

Data collection

We searched the PubMed, Embase and Cochrane Library databases using the search terms "cardiac sarcoidosis" and "immunosuppressive treatment" and "corticosteroid" (full search terms shown in supplement 1) and included all studies dealing with CS treatment from January 1980 to June 2019, excluding studies with tumour necrosis factor-α (TNF-α) antagonists' therapy because of their recent use in refractory CS cases after CT or IT failure [12].

Study selection

Studies were reviewed by two independent reviewers (J. Stievenart and V. Grobost). The inclusion criteria for relevant studies were as follows: English-language studies of CS diagnosed by endomyocardial biopsy, Heart Rhythm Society criteria [13], Japanese Ministry of Health and Welfare criteria [14] or World Association of Sarcoidosis and Other Granulomatous Diseases (WASOG) criteria [15]; follow-up of ⩾1 year; CT and/or IT (methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide or other conventional immunosuppressive agents) data on used schemes; and outcomes provided. We excluded studies that did not contain sufficient data or fulfil the inclusion criteria, and studies that treated patients with TNF-α antagonists. Studies were reviewed and included on the agreement of two independent reviewers (V. Grobost and J. Stievenart) using the title, abstract and full-text article if necessary; in cases of disagreement, we used a third reviewer (M. Ruivard). We included studies if there were enough data to supply a 2×2 table based on treatments used and outcomes. Duplicate publications were excluded, as were review articles, conference papers, isolated case reports, case series with fewer than five patients and letters.

Quality assessment and data extraction

Study quality was assessed independently by two reviewers (J. Stievenart and V. Grobost) using the Scottish Intercollegiate Guidelines Network (SIGN) checklist (supplement 2) [16]. Only studies with good or fair quality were included in the final review. Relevant information such as demographic characteristics, treatment, outcomes and relapse were abstracted.

End-points

The end-points were relapse (clinical and/or imaging relapse defined as onset of new CS manifestations or worsening of pre-existing manifestations), MACEs (defined as cardiac death, ventricular fibrillation, sustained ventricular tachycardia and hospitalisation for heart failure) and adverse drug events.

Results

Description of selected studies

A total of 1698 references were retrieved from PubMed, Embase and Cochrane Library databases. After abstract review and full-text assessment, 21 published studies were selected (figure 1). Authors, study design, diagnostic criteria, inclusion and exclusion criteria and sample size are summarised in table 1. Fourteen (66%) of the selected studies were Japanese. Only one study was prospective. Four studies were multicentric. No randomised control trial was retrieved. Using the SIGN overall assessment for cohort studies, the mean quality was 6.8 out of 14 (range 5–9). All studies provided good overall assessment.

Quantitative analysis

Baseline characteristics

Main baseline patient characteristics, including average age, mean follow-up, clinical outcomes and treatment, are summarised in table 2. The selected studies included 950 patients, whose average age ranged from 38 to 65 years. Mean follow-up ranged from 12 to 118.8 months. Prevalence of LV dysfunction or congestive heart failure ranged from 0% to 64% at baseline. Prevalence of atrioventricular block (AVB), ventricular tachycardia (VT), ventricular fibrillation (VF) and pacemaker or implantable cardioverter

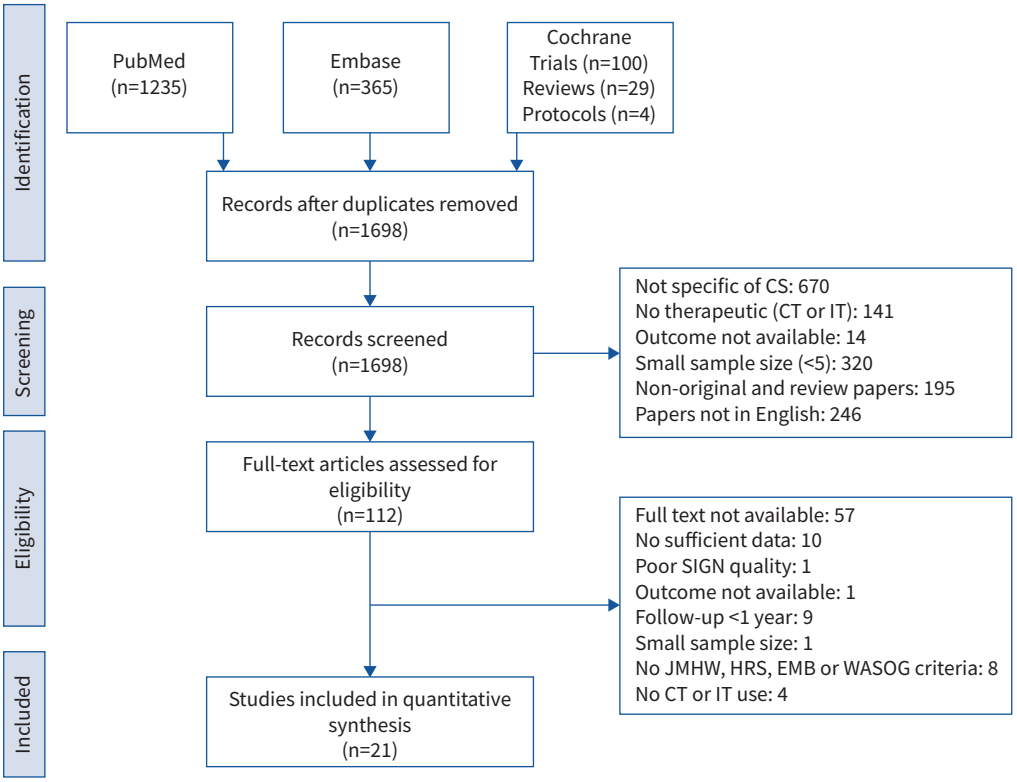

FIGURE 1 Systematic literature review and exclusions. CS: cardiac sarcoidosis; CT: corticosteroid therapy; IT: immunosuppressive therapy; SIGN: Scottish Intercollegiate Guidelines Network; JMWH: Japanese Ministry of Health and Welfare; HRS: Heart Rhythm Society; EMB: endomyocardial biopsy; WASOG: World Association of Sarcoidosis and Other Granulomatous Disorders.

defibrillator implantation varied depending on study design, from 2.4% to 91.9% of selected patients from retrieved studies. Data on implantation indications and devices were scarce.

Treatment regimen

Among the 950 patients, 709 were treated with corticosteroid alone and 155 with corticosteroids and immunosuppressive agents. CT regimens are listed in supplementary table S1. Prednisone dose ranged from 20 to 60 mg·day^{-1}, tapered every 6–8 weeks or over a 6-month period, until a maintenance dose of 5–10 mg·day^{-1} was reached, until relapse or the end of the study. Data on the duration of maintenance doses were unavailable. The immunosuppressive agents included cyclophosphamide, methotrexate, cyclosporin, azathioprine, mycophenolate mofetil and leflunomide. In two studies [23, 24], data on the chosen immunosuppressive agents were not provided. Antiarrhythmic drugs and classical cardiac treatment were given depending on study design and available data. In most cases, β-blockers, angiotensin-converting enzyme inhibitors, diuretics, digitalics and antiarrhythmic drugs were used. Treatment was prescribed individually and based on individual clinical and rhythmic findings, as were pacemakers or implantable cardioverter defibrillator devices.

Outcomes

CT alone

In 20 (95%) of the selected studies, 709 patients received CT. Nine studies (45%, n=351) provided data on relapses, representing an incidence of 34% (n=119) in patients who received CT alone (mean follow-up 15–118.8 months). Twelve studies (57%) did not provide clear data on relapses in the CT group. Only three studies (14%, n=73) provided data on MACEs (n=33), representing 45% of MACEs in patients treated by CT alone (mean follow-up 15–77.3 months).

ITs associated with CT

In nine (43%) of the selected studies, 155 patients received combined CT and IT. Only four studies (n=78) provided data on CS relapse, representing an incidence of 33% (n=26) in patients who received CT and IT

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TABLE 1 Qualitative extraction of selected studies

Reference	Year of publication	Countries	Number of centres	Study design	Chosen criteria for CS diagnosis	Inclusion criteria	Exclusion criteria	Sample size	SIGN score	SIGN overall assessment[#]
Myoren *et al.* [17]	2016	Japan	Single centre	Prospective	JMHW	Consecutive patients diagnosed with CS between June 2008 and December 2013	Acute heart failure, acute coronary syndrome, cancer, systemic inflammatory diseases, severe renal disease, smoker	30	6/14	+
Chapelon-Abric *et al.* [18]	2004	France	Multicentre	Retrospective	JMHW	Patients diagnosed with CS	None	41	8/14	+
Chapelon-Abric *et al.* [19]	2017	France	Single centre	Retrospective	JMHW	Patients diagnosed with CS	Possible or probable CS	59	6/14	+
Zhou *et al.* [20]	2017	USA	Single centre	Retrospective	WASOG	Patients diagnosed with CS	None	73	7/14	+
Orii *et al.* [21]	2015	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS	Coronary artery disease, any other cardiomyopathies, valvular disease	32	8/14	+
Takaya *et al.* [22]	2015	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS and patients with probable CS	Patients with certain CS not receiving CT, patients with probable CS receiving CT	47	8/14	+
Nagai *et al.* [23]	2015	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS	Coronary artery disease	83	9/14	+
Nagai *et al.* [24]	2016	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS	Coronary artery disease, follow-up <5 years	61	7/14	+
Kato *et al.* [25]	2003	Japan	Single centre	Retrospective	JMHW	AVB and CS diagnosis in the follow-up	LVEF <50%	20	7/14	+
Padala *et al.* [26]	2017	USA	Single centre	Retrospective	HRS	Patients diagnosed with CS	Unavailable follow-up data	30	7/14	+
Takaya *et al.* [27]	2015	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS	None	53	7/14	+
Chiu *et al.* [28]	2005	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS treated with steroid therapy	Patients without steroid therapy or regular follow-up, coronaropathy	43	7/14	+
Yazaki *et al.* [29]	2001	Japan	Multicentre	Retrospective	JMHW	Patients diagnosed with CS	None	95	7/14	+
Yodogawa *et al.* [30]	2013	Japan	Multicentre	Retrospective	JMHW	Patients diagnosed with CS	Significant coronary artery disease, known other cardiac diseases	15	6/14	+
Takaya *et al.* [31]	2014	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS	None	30	6/14	+

Continued

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TABLE 1 Continued

Reference	Year of publication	Countries	Number of centres	Study design	Chosen criteria for CS diagnosis	Inclusion criteria	Exclusion criteria	Sample size	SIGN score	SIGN overall assessment[#]
Naruse *et al.* [32]	2014	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS	Significant coronary artery disease, secondary myocardial disease (amyloidosis, arrhythmogenic right ventricular cardiomyopathy), RFCA before medication	37	8/14	+
Yalagudri *et al.* [11]	2017	India	Single centre	Retrospective	HRS	Diagnosis of probable CS based on HRS criteria, unexplained sVT, extracardiac histological diagnosis of CS, patchy uptake in the myocardium on cardiac PET scan	Tuberculosis, other causes of granulomatous myocarditis	18	5/14	+
Segawa *et al.* [33]	2016	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS	None	68	5/14	+
Ballul *et al.* [10]	2018	France	Single centre	Retrospective	HRS	Patients diagnosed with CS	None	36	5/14	+
Nagai *et al.* [34]	2014	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS	None	17	7/14	+
Kandolin *et al.* [35]	2015	Finland	Multicentre	Retrospective	WASOG	Newly diagnosed histologically proved CS, treatment naive, have undergone measurements of hs-cTnT or hs-cTnI at the time of diagnosis and after the start of treatment, have an estimated glomerular filtration >60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ by the MDRD study formula	None	62	8/14	+

CS: cardiac sarcoidosis; SIGN: Scottish Intercollegiate Guidelines Network; JMHW: Japanese Ministry of Health and Welfare; WASOG: World Association of Sarcoidosis and Other Granulomatous Disorders; CT: corticosteroid therapy; AVB: atrioventricular block; LVEF: left ventricular ejection fraction; HRS: Heart Rhythm Society criteria; RFCA: radiofrequency catheter ablation; sVT: sustained ventricular tachycardia; PET: positron emission tomography; hs-cTnT: high sensitivity troponin T; hs-cTnI: high sensitivity troponin I; MDRD: Modification of Diet in Renal Disease. [#]: "++" for good, "+" for fair, "−" for poor.

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TABLE 2 Patient baseline characteristics from selected studies

Reference	Year of publication	Sample size (n)	Male/ female (n/n)	Average age (years)	Mean follow-up (months)	LV dysfunction and/or CHF	PM or ICD implantation	AVB	VT/VF	Patients treated with CT	Patients treated with CT+IT	IT used
Myoren *et al.* [17]	2016	30	15/15	65±11	48	0	N/A	15 (50%)	19 (63%)	19 (63%)	0	None
Chapelon-Abric *et al.* [18]	2004	41	23/18	38 (18–66)	58 (7–312)	5 (12%)	1	7 (17%)	1	39 (95%)	13 (32%)	CYC, MTX, CIC
Chapelon-Abric *et al.* [19]	2017	59	39/20	42 (37–46)	60 (42–86)	38 (64%)	7 (12%)	15 (25%)	N/A	24 (41%)	35 (59%)	CYC, MTX, MMF
Zhou *et al.* [20]	2016	73	40/33	46 (20–71)	105.6	40 (55%)	54 (74%)	14 (19%)	26 (36%)	9 (12%)	54 (74%)	MTX, AZA, LEF, MMF, THA
Orii *et al.* [21]	2015	32	8/24	64±9	26±6	N/A	15 (47%)	15 (47%)	8 (25%)	10 (31%)	N/A	None
Takaya *et al.* [22]	2015	47	16/31	59±13	15 (1–149)	30 (64%)	10 (21%)	17 (36%)	12 (26%)	47 (100%)	N/A	None
Nagai *et al.* [23]	2015	83	24/59	60±12	91.2±52.8	11 (13%)	49 (59%)	33 (40%)	24 (29%)	67 (80%)	2	Unknown
Nagai *et al.* [24]	2016	61	17/44	59 (52–67)	118.8 (94.8–156)	9 (15%)	N/A	18 (30%)	22 (36%)	61 (100%)	1	Unknown
Kato *et al.* [25]	2003	20	1/19	63±9 (treated) 67.3±6.8 (not treated)	77.3±20.1 (treated) 80.4±45.9 (not treated)	N/A	17 (85%)	20 (100%)	0	7 (35%)	N/A	None
Padala *et al.* [26]	2017	30	16/14	58±10	33 (1–180)	14 (47%)	13 (43%)	5 (17%)	N/A	27 (90%)	10 (33%)	MTX, AZA, MMF
Takaya *et al.* [27]	2015	53	20/33	60±13	34 (1–149)	N/A	21 (40%)	22 (42%)	14 (26%)	42 (79%)	N/A	Unknown
Chiu *et al.* [28]	2005	43	16/27	48±14	88±48	21 (49%)	17 (40%)	N/A	N/A	43 (100%)	N/A	None
Yazaki *et al.* [29]	2001	95	34/61	53±13	68±42	36 (38%)	N/A	43 (45%)	17 (18%)	75 (79%)	N/A	None
Yodogawa *et al.* [30]	2013	15	2/13	59.9±9.7	85.2±63.6	5 (33%)	15 (100%)	15 (100%)	N/A	15 (100%)	N/A	None
Takaya *et al.* [31]	2014	30	10/20	61±12	12	10 (33%)	N/A	13 (43%)	12 (40%)	30 (100%)	N/A	None
Naruse *et al.* [32]	2014	37	11/26	56±11	39 (14–80)	19 (51%)	26 (70%)	10 (27%)	37 (100%)	34 (92%)	N/A	None
Yalagudri *et al.* [11]	2017	18	12/6	38±14	38.2 (10–75)	4 (22%)	7 (39%)	0	18 (100%)	18 (100%)	18 (100%)	MTX
Segawa *et al.* [33]	2016	68	18/50	57±11	66	10 (15%)	47 (69%)	29 (43%)	17 (25%)	68 (100%)	N/A	None

Continued

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TABLE 2 Continued

Reference	Year of publication	Sample size (n)	Male/ female (n/n)	Average age (years)	Mean follow-up (months)	LV dysfunction and/or CHF	PM or ICD implantation	AVB	VT/VF	Patients treated with CT	Patients treated with CT+IT	IT used
Ballul *et al.* [10]	2018	36	20/16	50.1	43.2 (12–182.4)	13 (39%)	13 (36%)	12 (33%)	N/A	24 (67%)	12 (33%)	AZA, MTX, CYC
Nagai *et al.* [34]	2014	17	3/14	N/A	N/A	8 (47%)	15 (88%)	13 (76%)	N/A	7 (41%)	10 (59%)	MTX
Kandolin *et al.* [35]	2015	62	14/48	48.6±11.9	17 (1–48)	10 (16%)	57 (92%)	33 (53%)	16 (26%)	62 (100%)	N/A	AZA, MTX

Data presented as mean±SD, mean (range) or n (%), unless otherwise stated. LV: left ventricular; CHF: congestive heart failure; PM: pacemaker; ICD: implantable cardiac defibrillator; AVB: atrioventricular block; VT: ventricular tachycardia; VF: ventricular fibrillation; CT: corticosteroid therapy; IT: immunosuppressive therapy; N/A: data not available; CYC: cyclophosphamide; MTX: methotrexate; CIC: ciclosporin; MMF: mycophenolate mofetil; AZA: azathioprine; LEF: leflunomide; THA: thalidomide.

(mean follow-up 39–66 months). Five studies did not provide clear data on relapse in this group. No study provided clear data on MACEs in patients who received combined CT and IT.

Relapses and MACEs

Data on MACEs and relapse rate are presented in table 3. Only one study [10] was designed to compare relapse rates between patients who received CT and CT+IT. Data on MACEs were not provided. Patients with cardiac relapse were more frequently male (p=0.052), less frequently black (p=0.008) and tended to be less frequently treated with IT (p=0.085). Frequency of cardiac relapse was lower in patients who received CT and IT at CS diagnosis than in patients who received CT alone (p=0.048). Among nine patients with severe cardiac relapse, seven (78%) received CT alone. MACEs were the chosen primary end-point in two studies [22, 27], indicating that MACEs during CS were significantly associated with initial presentation, including New York Heart Association class III or IV dyspnoea (p=0.024) and history of sustained VT or VF (p=0.002) [18, 36], and showing that the survival rate without MACEs was better in patients with a high degree of AVB as the initial presentation than in patients with VT and/or heart failure [27].

Cardiac or sudden death was the chosen primary end-point in three studies [17, 24, 29]. Myoren *et al.* [17] found that greater baseline urinary 8-hydroxy-2′-deoxyguanosine (p=0.020) and greater baseline B-natriuretic peptide (p=0.028) were significantly associated with cardiovascular-related death in multivariate analysis. Nagai *et al.* [24] investigated the effect of CT discontinuation on cardiac death. In this study, the continuation group had significantly better survival than the discontinuation group (p=0.035) with a maintenance CT dose of 5–10 mg·day^{-1} after nearly 10 years' mean follow-up. Yazaki *et al.* [29] found significantly better survival if patients had a baseline left ventricular ejection fraction (LVEF) ⩾50% (p<0.001). Nagai *et al.* [23] found that CT at diagnosis was the only multivariate negative predictive factor for all-cause death, or hospitalisation for heart failure or symptomatic arrhythmias.

Key points

The main results concerning AVB, VAs and LVEF are presented in table 4.

TABLE 3 Outcomes: relapses of cardiac sarcoidosis and MACEs in selected studies

Reference	Sample size (n)	Total relapses (n)	Corticosteroid alone			Immunosuppressor associated with corticosteroids		
			Treated patients[#]	Relapses[¶]	MACEs[+]	Treated patients[#]	Relapses[¶]	MACEs[+]
Myoren *et al.* [17]	30	N/A	19 (63%)	N/A	7 (36.8%)	0	N/A	N/A
Chapelon-Abric *et al.* [18]	41	9	39 (95%)	9 (23%)	N/A	13 (32%)	4 (31%)	N/A
Chapelon-Abric *et al.* [19]	59	23	24 (41%)	N/A	N/A	35 (59%)	11 (31%)	N/A
Zhou *et al.* [20]	73	N/A	9 (12%)	N/A	N/A	54 (74%)	N/A	N/A
Oriiet *al.* [21]	32	3	10 (31%)	3 (30%)	N/A	N/A	N/A	N/A
Takaya *et al.* [22]	47	25	47 (100%)	25 (53%)	25 (53%)	N/A	N/A	N/A
Nagai *et al.* [23]	83	N/A	67 (80%)	N/A	N/A	2	N/A	N/A
Nagai *et al.* [24]	61	11	60 (98%)	11 (16%)	N/A	1	N/A	N/A
Katoet *al.* [25]	20	9	7 (35%)	2 (28%)	1	N/A	N/A	N/A
Padala *et al.* [26]	30	6	27 (90%)	N/A	N/A	10 (33%)	N/A	N/A
Takaya *et al.* [27]	53	N/A	42 (79%)	N/A	N/A	N/A	N/A	N/A
Chiu *et al.* [28]	43	N/A	43 (100%)	N/A	N/A	N/A	N/A	N/A
Yazaki *et al.* [29]	95	N/A	75 (79%)	N/A	N/A	N/A	N/A	N/A
Yodogawa *et al.* [30]	15	N/A	15 (100%)	N/A	N/A	N/A	N/A	N/A
Takaya *et al.* [42]	30	N/A	30 (100%)	N/A	N/A	N/A	N/A	N/A
Naruse *et al.* [31]	37	22	34 (92%)	22 (65%)	N/A	N/A	N/A	N/A
Yalagudri *et al.* [11]	18	9	0	N/A	N/A	18 (100%)	9 (50%)	N/A
Segawa *et al.* [33]	68	20	68 (100%)	20 (29%)	N/A	N/A	N/A	N/A
Ballul *et al.* [10]	36	13	24 (67%)	11 (46%)	N/A	12 (33%)	2 (17%)	N/A
Nagai *et al.* [34]	17	N/A	7 (41%)	N/A	N/A	10 (59%)	N/A	N/A
Kandolin *et al.* [35]	62	16	62 (100%)	16 (100%)	N/A	N/A	N/A	N/A

Data presented as n (%), unless otherwise stated. MACEs: major adverse cardiac events (cardiac death, ventricular fibrillation, sustained ventricular tachycardia, hospitalisation for heart failure); N/A: data not available. [#]: percentage of the cohort; [¶]: percentage of relapses in the treated group; [+]: percentage of MACEs in the treated group.

TABLE 4 Outcome of AVB, VA and LVEF in selected studies

Key points	Reference	Outcomes	Comments
AVB	Yodogawa *et al.* [30] Takaya *et al.* [31]	High-degree heart block at presentation associated with recovery (p=0.040) and functional responsiveness (p=0.007)	High-degree heart block seems to be associated with recovery and was accessible to treatment
	Kato *et al.* [25]	AVB resolved in 4/7 treated patients *versus* 0/13 untreated patients (p<0.05)	
VA	Kato *et al.* [25]	CT-treated patients (77.3±20.1 months): 1 VT for 7 patients Untreated patients (80.4±45.9 months): 8 VTs for 13 patients (p<0.05)	VTs were accessible to treatment
	Padala *et al.* [26] Naruse *et al.* [32] Segawa *et al.* [33]	VTs or VAs were significantly associated with lower LVEF at baseline	VTs or VAs were associated with lower LVEF
	Yalagudri *et al.* [11]	Patients with myocardial inflammation seen at FDG-PET had VT recurrence while patients without FDG-PET uptake did not show evidence of VT recurrence	VTs were positively associated with myocardial FDG-PET uptake
LVEF	Chiu *et al.* [28]	Patients with baseline LVEF between 30% and 55% tended to have a significant benefit on LVEDVI (p=0.018) and on LVEF (p=0.008) after CT, and a significant improvement of LVEF after CT treatment compared with patients with baseline LVEF⩾50% or LVEF<30% (p<0.0001)	LVEF was improved with CT, especially in patients with moderate impairment (LVEF between 30% and 55%)
	Zhou *et al.* [20]	15/27 patients with baseline LVEF<40% had improvement of LVEF after CT	Even severe LVEF impairment might improve with CT

AVB: atrioventricular block; CT: corticosteroid therapy; LVEDVI: left ventricular end diastolic volume index; LVEF: left ventricular ejection fraction; VA: ventricular arrhythmia; VT: ventricular tachycardia.

Adverse drug events

Available data on adverse drug events were scarce. Only four studies (19%, n=156) provided data on adverse events under CT alone or combined with IT. Ballul *et al.* [10] provided adverse event data by treatment group, and no difference was found in infection rates between CT and CT+IT groups.

Discussion

In this study, we investigated the current literature on conventional CT and IT for CS. Reviews and expert consensus consider that LV dysfunction, arrhythmias and prevention of sudden cardiac death in CS should be managed in the same way as in patients without CS, following national and international recommendations [8, 13]. Treatment of LV dysfunction is based on angiotensin receptor II blockers, aldosterone inhibitors and diuretics. β-blockers should be used prudently owing to the risk of severe AVB in some cases. Severe AVB should be detected as soon as possible in the course of CS so that patients can benefit from cardiac device implantation (pacemaker) [37], even before IT. In refractory VA, mapping and radiofrequency ablation might be effective in some cases [38, 39].

Corticosteroids are the mainstay treatment of CS and can notably improve outcomes for recurrent LVEF, AVB and VA [26, 30], or imaging extension of the disease [40]. CT dose and duration remain unclear. In a Japanese cohort, there was no impact on outcomes between high *versus* low starting dose of CT [29]. Padala *et al.* [26] emphasised the necessity of early CT initiation after CS diagnosis. Yodogawa *et al.* [41] described less ventricular extrasystole and VT after CT in patients with LVEF ⩾35%. In our systematic review, different initial doses and tapering regimens were used. Some studies used prednisone 20–60 mg·day^{-1} as the initial dose, tapered over a period of 6 weeks to 12 months up to a maintenance dose of 5–10 mg·day^{-1}, without data on CT duration and heterogeneous CT regimens. Nonetheless, all these data taken together emphasise the importance of early initiation of CT after CS diagnosis, before the establishment of myocardial scars and worsening LVEF.

This systematic review reveals that IT is used in accordance with the design of the study concerned, analogous to extracardiac sarcoidosis. Indications for IT are generally for corticosteroid sparing, more severe clinical presentation at diagnosis or add-on therapy when relapse occurs. Only a few studies used combined IT and CT [10, 11, 20, 34] in a pre-specified method. The most-used immunosuppressant was methotrexate. Ballul *et al.* [10] found lower survival, although not significant, without relapse in the IT group, whereas IT combined with CT at CS diagnosis was significantly associated with fewer relapses than using CT alone. Nagai *et al.* [34] compared low-dose CT (5–15 mg·day^{-1}) to low-dose CT associated with

methotrexate (6 mg·week^{-1}). LVEF was significantly better at 3 years' follow-up in the methotrexate group (44.5±13.8% *versus* 60.7±14.3%) but not at 5 years' follow-up (45.7±15.5% *versus* 53.6±13.3%). Ten studies (48%) stated use of IT in reported patients; only nine studies gave data on patients treated by IT and four studies indicated relapse rate under IT. No data on MACEs were provided in any study using IT. Only one study [10] provided comparative data on adverse events in patients receiving CT alone and in combination with IT, and there was no significant difference. In this systematic review, we found a similar rate of relapse in patients receiving CT alone (34%) and combined with IT (33%) but the two groups could not be compared. However, it was not possible to draw any conclusions on those rates due to the heterogeneity of the study design, follow-up, treatment schemes, different end-points and missing data. For these reasons, reliable meta-analysis on CS treatments is impossible. There is a clear lack of long-term outcomes in CS, which is an unpredictable disease.

In the literature, methotrexate seems to be the first-choice immunosuppressant for extracardiac sarcoidosis, and as second-line treatment in steroid-refractory cases or in the presence of steroid-associated adverse events in WASOG recommendations (2b level of evidence) [42]. In 2013, Vorselaars *et al.* [43] published a retrospective case–control study that compared methotrexate and azathioprine for steroid-sparing effect, pulmonary function and adverse effects as second-line treatment of pulmonary sarcoidosis. They found similar significant steroid sparing and adverse effects, except for a higher infection rate with azathioprine, in a 1-year follow-up study. To our knowledge, there is no study providing such information for CS.

In our systematic review, only 11 studies provided relapse rates, and only two established MACEs as a clear end-point, which might underestimate the relapse rate and MACEs in CS.

Recently, cohort studies were published on TNF-α antagonist use in refractory CS cases after CT and IT failure. In these cohorts, adalimumab suppressed fluorodeoxyglucose uptake on positron emission tomography [44] in 66% of responders under infliximab therapy in 36 patients refractory to CT and IT [12], and there was a corticosteroid sparing effect with adalimumab or infliximab without worsening of LVEF [45]. No data are published in early therapy of CS with TNF-α antagonists.

Several limitations must be mentioned. No randomised control trial was found, only one study was prospective and most studies took place in Japanese centres. These limitations prevent us from extrapolating recommendations to Western European countries and Caucasian patients because CS presentation can show ethnic and national differences [3]. The lack of prospective or randomised control trials could largely be explained by the urgent need for treatment when CS is diagnosed and the scarcity of CS in each centre. There were only cohort studies with fair quality according to the SIGN rating. Another limitation was the heterogeneity of the end-points, which did not allow comparison between outcomes. Strong end-points, such as relapse and MACEs, were selected in only three studies [10, 22, 24] and some studies were excluded based on imaging changes and because they did not provide sufficient data on end-points such as relapse or MACEs. Heterogeneous treatment regimens and a lack of data made it difficult to interpret the immunosuppressive effects on CS disease course, steroid sparing and comparison between CT alone and in combination with IT. Finally, data on adverse drug events were provided in only four studies, making comparison difficult between CT and IT in terms of safety.

Taking into account these results, and the potential life-threatening issues in CS, we suggest an early CT of 0.5–1 mg·kg^{-1}·day^{-1} with a 3–6 months tapering scheme in case of clinical and imaging remission, and an adjunctive therapy with a steroid-sparing agent such as methotrexate at usual dose. We cannot clearly select patients who will most benefit from IT; therefore, IT prescription should be wide and adapted to each patient's conditions.

Patients' follow-up should be based on initial presentation (cardiac failure and/or rhythmic presentation), and further studies should split patients into groups upon their initial presentation based on function and rhythm.

Recently, studies on TNF-α antagonists have shown interesting outcomes in patients with resistant or relapsing CS [12, 44–47]. Further studies, including comparative groups between CT-, IT- and TNF-α antagonist-treated patients, are needed to clarify which treatment schemes could be recommended.

Conclusion

Currently, CS is a life-threatening condition and treatment is based on corticosteroids, which should be administered as soon as possible after the diagnosis of cardiac involvement in sarcoidosis. Conventional IT

as add-on therapy or a steroid-sparing agent seems to have a good tolerance profile and safety, but its efficacy on outcomes in terms of relapse rate and major cardiac events is not clear. Heterogeneity in study design prevents us from making any clear recommendations. Further studies with homogenous groups, comparisons between the different treatments schemes and with reproducible strong end-points are needed.

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