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 MACEs, 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

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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, SADIK 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 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
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, \(\beta\)-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.
| 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-Ablic et al. [18] | 2004                | France     | Multicentre       | Retrospective | JMHW                             | Patients diagnosed with CS                                                        | None                                                                                   | 41          | 8/14        | +                      |
| Chapelon-Ablic 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        | +                      |
| Ori et al. [21]    | 2015                | Japan      | Single centre     | Retrospective  | JMHW                             | Patients diagnosed with CS                                                        | Coronary artery disease, any other cardiomyopathies, valvular disease                  | 32          | 8/14        | +                      |
| Takaoka 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        | +                      |
| Takaoka 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, coronaryopathy                  | 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        | +                      |
| Takaoka et al. [31] | 2014                | Japan      | Single centre     | Retrospective  | JMHW                             | Patients diagnosed with CS                                                        | None                                                                                   | 30          | 6/14        | +                      |

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-cTnl at the time of diagnosis and after the start of treatment, have an estimated glomerular filtration >60 mL/min·1.73 m² 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-cTnl: high sensitivity troponin I; MDRD: Modification of Diet in Renal Disease. *: “+” for good, “++” for fair, “−” for poor.
| 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.     | 2016                | 30              | 15/15              | 65±11              | 48                      | 0                         | N/A                    | 15  | (50%)| 19 (63%)                 | 19 (63%)                   | None    |
| Chapelon-abric et al. | 2004               | 41              | 23/18              | 38 (18–66)         | 58 (7–312)              | 5 (12%)                  | 1                      | 7   | (17%)| 1                        | 39 (95%)                   | CYC, MTX, CIC CYC, MTX, MMF |
| Chapelon-abric et al. | 2017               | 59              | 39/20              | 42 (37–46)         | 60 (42–86)              | 38 (64%)                 | 7 (12%)                | 15  | (25%)| N/A                      | 24 (41%)                   | CYC, MTX, MMF |
| Zhou et al.       | 2016                | 73              | 40/33              | 46 (20–71)         | 105.6                   | 40 (55%)                 | 54 (74%)               | 14  | (19%)| 26 (36%)                 | 9 (12%)                    | CYC, MTX, MMF, LEF, MMF, THA |
| Oh et al.         | 2015                | 32              | 8/24               | 64±9               | 26±6                    | N/A                      | 15 (47%)               | 15  | (47%)| 8 (25%)                  | 10 (31%)                   | N/A     |
| Takaya et al.     | 2015                | 47              | 16/31              | 59±13              | 15 (1–149)              | 30 (64%)                 | 10 (21%)               | 17  | (36%)| 12 (26%)                 | 47 (100%)                  | N/A     |
| Nagai et al.      | 2015                | 83              | 24/59              | 60±12              | 91.2±52.8               | 11 (13%)                 | 49 (59%)               | 33  | (40%)| 24 (29%)                 | 67 (80%)                   | Unknown |
| Nagai et al.      | 2016                | 61              | 17/44              | 59 (52–67)         | 118.8 (94.8–156)        | 9 (15%)                  | N/A                    | 18  | (30%)| 22 (36%)                 | 61 (100%)                  | Unknown |
| Kato et al.       | 2003                | 20              | 1/19               | 63±9 (treated)     | 77.3±20.1 (treated)     | N/A                      | 17 (85%)               | 20  | (100%)| 0                        | 7 (35%)                    | None    |
| Padala et al.     | 2017                | 30              | 16/14              | 58±10              | 33 (1–180)              | 14 (47%)                 | 13 (43%)               | 5   | (17%)| N/A                      | 27 (90%)                   | MTX, AZA, MMF |
| Takaya et al.     | 2015                | 53              | 20/33              | 60±13              | 34 (1–149)              | N/A                      | 21 (40%)               | 22  | (42%)| 14 (26%)                 | 42 (79%)                   | N/A     |
| Chiu et al.       | 2005                | 43              | 16/27              | 48±14              | 88±48                   | 21 (49%)                 | 17 (40%)               | N/A | N/A | N/A                      | 43 (100%)                  | N/A     |
| Yazaki et al.     | 2001                | 95              | 34/61              | 53±13              | 68±42                   | 36 (38%)                 | N/A                    | 43  | (45%)| 17 (18%)                 | 75 (79%)                   | N/A     |
| Yoodogawa et al.  | 2013                | 15              | 2/13               | 59.9±9.7           | 85.2±63.6               | 5 (33%)                  | 15 (100%)              | 15  | (100%)| N/A                      | 15 (100%)                  | N/A     |
| Takaya et al.     | 2014                | 30              | 10/20              | 61±12              | 12                      | 10 (33%)                 | N/A                    | 13  | (43%)| 12 (40%)                 | 30 (100%)                  | N/A     |
| Naruse et al.     | 2014                | 37              | 11/26              | 56±11              | 39 (14–80)              | 19 (51%)                 | 26 (70%)               | 10  | (27%)| 37 (100%)                | 34 (92%)                   | N/A     |
| Yalagudri et al.  | 2017                | 18              | 12/6               | 38±14              | 38.2 (10–75)            | 4 (22%)                  | 7 (39%)                | 0   | 18 (100%)                | 18 (100%)                  | MTX     |
| Segawa et al.     | 2016                | 68              | 18/50              | 57±11              | 66                      | 10 (15%)                 | 47 (69%)               | 29  | (43%)| 17 (25%)                 | 68 (100%)                  | N/A     |

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) $\geq$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 patients¹    | Relapses²  | MACEs²        | treated patients¹ | Relapses² | MACEs²         |
| 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           |
| Orih et 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           |
| Kato et al. [25]   | 20             | 9                 | 7 (35%)              | 2 (28%)   | 1             | N/A             | N/A       | N/A           |
| PADAKA 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           |
| CHU et al. [28]    | 43             | N/A               | 43 (100%)            | N/A       | N/A           | N/A             | N/A       | N/A           |
| YAMAGI et al. [29] | 95             | N/A               | 75 (79%)             | N/A       | N/A           | N/A             | N/A       | N/A           |
| YODOSHI 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           |
| YALAGURU et al. [11] | 18         | 9                 | 0                    | N/A       | N/A           | 18 (100%)       | 9 (50%)   | N/A           |
| SEGAWA et al. [32] | 68             | 20                | 68 (100%)            | 20 (29%)  | N/A           | N/A             | N/A       | N/A           |
| BALLU 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. ¹: percentage of the cohort; ²: percentage of relapses in the treated group; ³: percentage of MACEs in the treated group.
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]. PARADISE et al. [26] emphasised the necessity of early CT initiation after CS diagnosis. YODAGAWA 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

| TABLE 4 Outcome of AVB, VA and LVEF in selected studies |
|----------------|------------------|--------------------------|--------------------------|
| **Key points** | **Reference** | **Outcomes** | **Comments** |
| AVB | YODAGAWA et al. [30] | 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 |
| | TAKARA et al. [31] | 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] | VTs or VAs were significantly associated with lower LVEF at baseline | VTs or VAs were associated with lower LVEF |
| | NARUSE et al. [32] | | |
| | SEGAWA et al. [33] | | |
| | 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.
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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