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Early View

Review

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

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

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Brief Summary

We did a systematic review of corticosteroid and conventional immunosuppressive therapies use in cardiac sarcoidosis in order to define immunosuppressive place in treatment scheme. Corticosteroid remain the mainstay treatment in cardiac sarcoidosis. Other immunosuppressive therapies may be interesting as add-on therapy to corticosteroid, in order to prevent relapse but data are lacking about therapeutic schemes, the time to introduced, the benefits to prevent relapse, adverse events, cardiac death, ventricular fibrillation, sustained ventricular tachycardia, and hospitalization for heart failure in cardiac sarcoidosis.

Abstract

BACKGROUND: Cardiac sarcoidosis (CS) is a life-threatening condition in which clear recommendations are lacking. We aimed to review systematically 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/or standard immunosuppressive therapies for CS which provided at least fair SIGN overall assessment of quality and analyse the relapse rate, major cardiac adverse events (MACEs) and adverse events. We base our methods on Prisma statement and checklist.

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

CONCLUSIONS: 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.

1. 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% to 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 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. Corticosteroids remain 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.* published a systematic review of corticosteroid therapy (CT) as the mainstay treatment for CS[9].

We conducted a systematic review of the literature on CT and/or immunosuppressive therapy (IT) of 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, hospitalization for heart failure), as well as to study adverse drug events.

2. Methods

2.1. 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 Appendix 1) and included all studies dealing with CS treatment, from January 1980 to June 2019, excluding studies with tumour necrosis factor (TNF)α antagonists’ therapy, because of their recent use in refractory CS cases, after CT or IT failure[12]. The search terms are specified in Supplemental Methods 1.

2.2. Study selection

Studies were reviewed by two independent reviewers (JS and VG). The inclusion criteria for relevant studies were: 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, outcomes. We excluded studies if they did not contain sufficient data or fulfil the inclusion criteria, and studies that treated patients with TNFα antagonists. Studies were reviewed and included if two independent reviewers (VG & JS) agreed, using title, abstract and full-text article if necessary; if they did not agree, we used a third reviewer (MR). We included studies if there were enough data to supply a 2x2 table based on treatments used and outcomes. Duplicate publications were excluded, as were review articles, conference papers, isolated case reports, case series with <5 patients, and letters.

2.3. Quality assessment and data extraction

Study quality was assessed independently by two reviewers (JS and VG), using the Scottish Intercollegiate Guidelines Network (SIGN) checklist (Supplemental Methods 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.

2.4. Endpoints

The endpoints 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 hospitalization for heart failure); and adverse drug events.

3. Results

3.1. 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 summarized in Table 1. Fourteen (66%) of the selected studies were Japanese. Only one study was prospective. Four studies were multicentric. No randomized control trial was retrieved. Using the SIGN overall assessment for cohort studies, the mean quality was 6.8/14 (range 5–9). All studies provided good overall assessment.

3.2. Quantitative analysis

***Baseline characteristics*.** Main baseline patient characteristics, including average age, mean follow-up, clinical outcomes, and treatment are summarized 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 left ventricular dysfunction or congestive heart failure ranged from 0 to 64% at baseline. Prevalence of atrioventricular block (AVB), ventricular tachycardia (VT), and ventricular fibrillation (VF), and pacemaker or implantable cardioverter defibrillator implantation varied depending on study design, from 2.4 to 91.9% of selected patients toward retrieved studies. Data on implantations 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 Supplemental Table 1. Prednisone dose ranged from 20 to 60 mg/day, tapered every 6–8 weeks or over a 6-month period, until a maintenance dose of 5–10 mg/day 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[17,18], data on the chosen immunosuppressive agents were not provided. Antiarrhythmic drugs (AADs) 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 AADs were used. Treatment was prescribed individually and based on individual clinical and rhythmic findings, as were pacemakers or implantable cardioverter defibrillator devices.

Outcomes

Corticosteroid alone. In 20 (95%) of the selected studies, 709 patients received CT. Nine (45%) studies (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 (57%) studies 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).

Immunosuppressive therapies 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 (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 relapses rate between patients who received CT and CT plus 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 tend to be less frequently treated with immunosuppressive drugs (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 endpoint in two studies[19,20], indicating that MACEs during CS were significantly associated with initial presentation including NYHA class III or IV dyspnoea (p=0.024), and history of sustained VT (sVT) or VF (p=0.002)[36,37], and showing that 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.[20]

Cardiac or sudden death was the chosen primary endpoint in three studies.[18,21,22] Myoren *et al.*[21] 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.*[18] investigated the effect of CT discontinuation on cardiac death. In this study, the continuation group had a significantly better survival than the discontinuation group (p=0.035) with a maintenance CT dose of 5–10 mg/day after nearly 10 years' mean follow-up. Yazaki *et al.*[22] found significantly better survival if patients had a baseline LVEF ≥50% (p<0.001). Nagai *et al.*[17] found that CT at diagnosis was the only multivariate negative predictive factor for all-cause death, or hospitalization for heart failure or symptomatic arrhythmias.

Key points. Main results concerning AVB, VAs and LVEF are presented in Table 4.

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.

4. 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.[13,23] Treatment of LV dysfunction is

based on angiotensin receptor II blockers, aldosterone inhibitors, and diuretics. Beta-blockers should be used prudently due 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)[24], even before IT. In refractory VA, mapping and radiofrequency ablation might be effective in some cases.[25,26]

Corticosteroids are the mainstay treatment of CS and can notably improve outcomes for recurrent LVEF, AVB and VA[27,28], or imaging extension of the disease.[46] CT dose and duration remain unclear. In a Japanese cohort, there was no impact on outcomes between high versus low starting dose of CT.[22] Padala *et al.* emphasized the necessity of early CT initiation after CS diagnosis.[27] Yodogawa *et al.* described less ventricular extrasystole and VT after CT in patients with LVEF ≥35%.[29] In our systematic review, different initial doses and tapering regimens were used. Some studies used prednisone 20–60 mg/day as the initial dose, tapered over a period of 6 weeks to 12 months up to a maintenance dose of 5–10 mg/day, without data on CT duration and heterogeneous CT regimens. Nonetheless, all these data taken together emphasize the utility 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 of IT are generally for corticosteroids sparing, more severe clinical presentation at diagnosis, or add-on therapy when relapse occurs. Only a few studies used combined IT and CT[10,11,30,31] in a pre-specified method. The most-used immunosuppressant is methotrexate. Ballul *et al.*[10] found lower survival, but not significantly, 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.*[31] compared low-dose CT (5–15 mg/day) to low-dose CT associated with methotrexate (6 mg/week). LVEF was significantly better at 3 years' follow-up in the methotrexate group (44.5%±13.8% vs

60.7%±14.3) but not at 5 years' follow-up (45.7%±15.5% vs 53.6%±13.3). Ten (48%) studies 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 endpoints, 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 ranked as second-line treatment in steroid-refractory cases or in the presence of steroid-associated adverse events in WASOG recommendations (2b level of evidence).[32] In 2013, Vorselaars *et al.* 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.[33] 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 endpoint, which might underestimate the relapse rate and MACEs in CS.

Recently, cohort studies were published on TNFα antagonists use in refractory CS cases after CT and IT failure. These cohorts showed an interesting effect of adalimumab on suppressing fluorodeoxyglucose uptake on positron emission tomography,[34] 66% of responders under infliximab therapy in 36 patients refractory to CT and IT[12] and an interesting corticosteroid sparing effect with adalimumab or infliximab without worsening of LVEF[35] . No data are published in early therapy of CS with TNFα antagonists.

Several limitations must be mentioned. No randomized control trial was found, only one study was prospective and most studies took place in Japanese centres. These remarks prevent us from drawing any clear extrapolation or recommendations to Western European countries and Caucasian since CS presentation can show ethnic and national differences.[3] The lack of prospective or randomized control trials could largely be explained by the urgent need of 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 endpoints, which did not allow comparison between outcomes. Strong endpoints, such as relapse and MACEs were selected in only three studies[10,18,19] and some studies were excluded because based on imaging changes and did not bring sufficient data on endpoints 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 corticosteroid treatment at 0.5 to 1 mg/kg/day with a 3 to 6 months tapering scheme in case of clinical and imaging remission, and an adjunctive therapy by a steroid sparing agent such as methotrexate at usual dose. We cannot clearly select patients who will most benefit of 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 probably split patients in groups upon their initial presentation (function and rhythm).

Recently, studies on TNFα antagonists have shown interesting outcomes in patients with resistant or relapsing CS. [47-51] Further studies, including comparative groups between CT, IT and TNFα antagonists' treated patients, are needed to clarify which treatments schemes could be recommended.

5. 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 steroid-sparing agents 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 endpoints are needed.

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None.

Availability of data and materials

The datasets obtained and/or analysed during the current study are available from the corresponding author on reasonable request.

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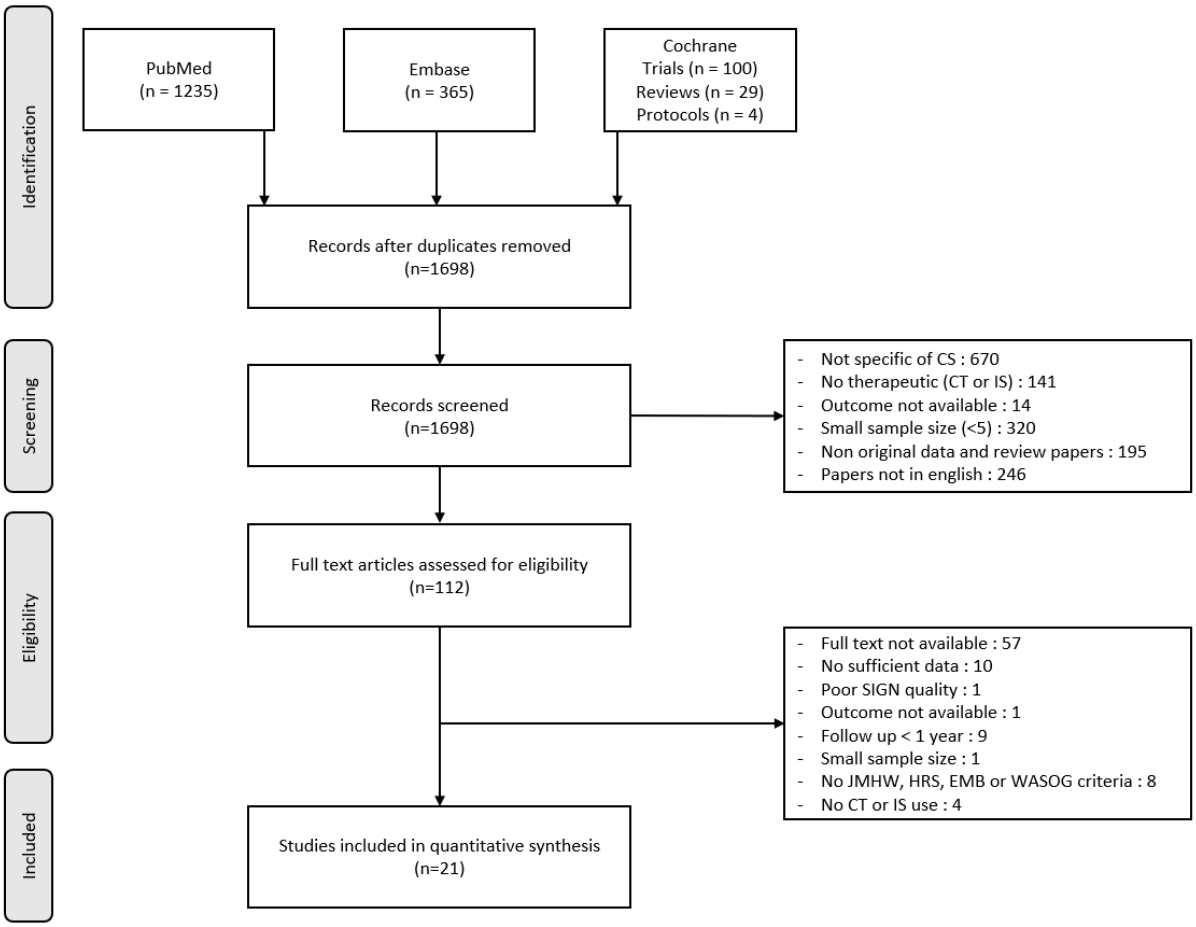


Figure 1. Systematic literature review and exclusions

Table 1. Qualitative extraction of selected studies

First author	Year of publication	Countries	Number of centres	Study design	Chosen critera for CS diagnosis	Inclusion criteria	Exclusion criteria	Sample size	SIGN score	SIGN overall assessment
Myoren (21)	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 (37)	2004	France	Multicentre	Retrospective	JMHW	Patients diagnosed with CS	None	41	8/14	+
Chapelon-Abric (38)	2017	France	Single centre	Retrospective	JMHW	Patients diagnosed with CS	Possible or probable CS	59	6/14	+
Zhou (30)	2017	USA	Single centre	Retrospective	WASOG	Patients diagnosed with CS	None	73	7/14	+
Orii (39)	2015	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS	Coronary artery disease, any other cardiomyopathies, valvular disease	32	8/14	+
Takaya (19)	2015	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS and patients with probable CS	Patients with certain CS not receiving CT and patients with probable CS receiving CT	47	8/14	+
Nagai (17)	2015	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS	Coronary artery disease	83	9/14	+
Nagai (18)	2016	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS	Coronary artery disease, follow up less than 5 years	61	7/14	+
Kato (40)	2003	Japan	Single centre	Retrospective	JMHW	AVB and CS diagnosis in the follow up	LVEF <50%	20	7/14	+
Padala (27)	2017	USA	Single centre	Retrospective	HRS	Patients diagnosed with CS	Unavailable follow up data	30	7/14	+
Takaya (20)	2015	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS	None	53	7/14	+
Chiu (41)	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 (22)	2001	Japan	Multicentre	Retrospective	JMHW	Patients diagnosed with CS	None	95	7/14	+
Yodogawa (28)	2013	Japan	Multicentre	Retrospective	JMHW	Patients diagnosed with CS	Significant coronary artery disease, known other cardiac diseases	15	6/14	+
Takaya (42)	2014	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS	None	30	6/14	+
Naruse (43)	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 (11)	2017	India	Single centre	Retrospective	HRS	Diagnosis of probable CS based on HRS criteria, unexplained sVT, extra-cardiac histological diagnosis of CS, patchy uptake in the myocardium on cardiac PET scan.	tuberculosis, other causes of granulomatous myocarditis	18	5/14	+
Segawa (44)	2016	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS	None	68	5/14	+
Ballul (10)	2018	France	Single centre	Retrospective	HRS	Patients diagnosed with CS	None	36	5/14	+
Nagai (31)	2014	Japan	Single centre	Retrospective	JMHW	Patients diagnosed with CS	None	17	7/14	+
Kandolin (45)	2015	Finland	Multicentre	Retrospective	WASOG	Newly diagnosed histologically proved CS, treatment naive, have undergone measurements of hs-cTnT or hs-cTnI at the time diagnosis and after the start of treatment, have an estimated glomerular filtration >60 ml/min/1.73 m2 by the Modification of Diet in Renal Disease (MDRD) Study formula	None	62	8/14	+

SIGN overall assessment: "++" for good, "+" for fair, "–" for poor. AVB, atrioventricular block; CS, cardiac sarcoidosis; CT, corticosteroid therapy; hs-cTnI: high sensitivity Troponin I; hs-cTnT: high sensitivity Troponin T; HRS, Heart Rhythm Society criteria; JMHW, Japanese Ministry of Health and Welfare; LVEF, Left Ventricular Ejection Fraction; RFCA: Radiofrequency Catheter Ablation; SIGN, Scottish Intercollegiate Guidelines Network; WASOG, World Association of Sarcoidosis and other Granulomatous Disorders.

Table 2. Patient baseline characteristics from selected studies

First author	Year of publication	Sample size	Male/female	Average age	Mean follow-up (months)	Left ventricular dysfunction and/or CHF	PM or ICD implantation	AVB	VT/VF	Number of patients treated with corticosteroid alone	Number of patients treated with steroid plus immunosuppressor	Immunosuppressor used
Myoren (21)	2016	30	15/15	65 ± 11	48	0	N/A	15 (50%)	19 (63%)	19 (63%)	0	None
Chapelon-Abric (37)	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 (38)	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 (30)	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 (39)	2015	32	8/24	64 ± 9	26 ± 6	N/A	15 (47%)	15 (47%)	8 (25%)	10 (31%)	N/A	None
Takaya (19)	2015	47	16/31	59 ± 13	15 (1-149)	30 (64%)	10 (21%)	17 (36 %)	12 (26%)	47 (100%)	N/A	None
Nagai (17)	2015	83	24/59	60 ± 12	91,2 ± 52,8	11 (13%)	49 (59%)	33 (40%)	24 (29%)	67 (80%)	2	Unknown
Nagai (18)	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 (40)	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 (27)	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 (20)	2015	53	20/33	60 ± 13	34 (1-149)	N/A	21 (40%)	22 (42%)	14 (26%)	42 (79%)	N/A	Unknown
Chiu (41)	2005	43	16/27	48 ± 14	88 ± 48	21 (49%)	17 (40%)	N/A	N/A	43 (100%)	N/A	None
Yazaki (22)	2001	95	34/61	53 ± 13	68 ± 42	36 (38%)	N/A	43 (45%)	17 (18%)	75 (79%)	N/A	None
Yodogawa (28)	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 (42)	2014	30	10/20	61 ± 12	12	10 (33%)	N/A	13 (43%)	12 (40%)	30 (100%)	N/A	None
Naruse (43)	2014	37	11/26	56 ± 11	39 (14 - 80)	19 (51%)	26 (70%)	10 (27%)	37 (100%)	34 (92%)	N/A	None
Yalagudri (11)	2017	18	12/6	38 ± 14	38,2 (10-75)	4 (22%)	7 (39%)	0 (0%)	18 (100%)	18 (100%)	18 (100%)	MTX
Segawa (44)	2016	68	18/50	57 ± 11	66	10 (15%)	47 (69%)	29 (43%)	17 (25%)	68 (100%)	N/A	None
Ballul (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 (31)	2014	17	3/14	N/A	N/A	8 (47%)	15 (88%)	13 (76%)	N/A	7 (41%)	10 (59%)	MTX
Kandolin (45)	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 given as mean ± SD or n (%). AVB, atrioventricular block; AZA, azathioprine; CHF, congestive heart failure; CIC, ciclosporin; CYC, cyclophosphamide; ICD, implantable cardiac defibrillator; LEF, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; N/A, data not available; PM, pacemaker; THA, thalidomide; VF, ventricular fibrillation; VT, ventricular tachycardia.

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

First author	Sample size	Total Number of relapses	Corticosteroid alone			Immunosuppressor associated with corticosteroids		
			Number of treated Patients (%)[1]	Number of relapses (%)†	MACEs (%)‡	Number of treated Patients (%)[1]	Number of relapses (%)†	MACEs (%)‡
Myoren (21)	30	N/A	19 (63%)	N/A	7 (36.8%)	0	N/A	N/A
Chapelon-Abric (37)	41	9	39 (95%)	9 (23%)	N/A	13 (32%)	4 (31%)	N/A
Chapelon-Abric (38)	59	23	24 (41%)	N/A	N/A	35 (59%)	11 (31%)	N/A
Zhou (30)	73	N/A	9 (12%)	N/A	N/A	54 (74%)	N/A	N/A
Orii (39)	32	3	10 (31%)	3 (30%)	N/A	N/A	N/A	N/A
Takaya (19)	47	25	47 (100%)	25 (53%)	25 (53%)	N/A	N/A	N/A
Nagai (17)	83	N/A	67 (80%)	N/A	N/A	2	N/A	N/A
Nagai (18)	61	11	60 (98%)	11 (16%)	N/A	1	N/A	N/A
Kato (40)	20	9	7 (35%)	2 (28%)	1	N/A	N/A	N/A
Padala (27)	30	6	27 (90%)	N/A	N/A	10 (33%)	N/A	N/A
Takaya (20)	53	N/A	42 (79%)	N/A	N/A	N/A	N/A	N/A
Chiu (41)	43	N/A	43 (100%)	N/A	N/A	N/A	N/A	N/A
Yazaki (22)	95	N/A	75 (79%)	N/A	N/A	N/A	N/A	N/A
Yodogawa (28)	15	N/A	15 (100%)	N/A	N/A	N/A	N/A	N/A
Takaya (42)	30	N/A	30 (100%)	N/A	N/A	N/A	N/A	N/A
Naruse (43)	37	22	34 (92%)	22 (65%)	N/A	N/A	N/A	N/A
Yalagudri (11)	18	9	0	N/A	N/A	18 (100%)	9 (50%)	N/A
Segawa (44)	68	20	68 (100%)	20 (29%)	N/A	N/A	N/A	N/A
Ballul (10)	36	13	24 (67%)	11 (46%)	N/A	12 (33%)	2 (17%)	N/A
Nagai (31)	17	N/A	7 (41%)	N/A	N/A	10 (59%)	N/A	N/A
Kandolin (45)	62	16	62 (100%)	16 (100%)	N/A	N/A	N/A	N/A

Data given as n (%). [1]: percentage of the cohort; †: percentage of relapses in the treated group; ‡: percentage of MACEs in the treated group. MACEs: major adverse cardiac events (cardiac death, ventricular fibrillation, sustained ventricular tachycardia, hospitalization for heart failure); N/A, data not available.

Table 4. Outcome of AVB, VA and LVEF in selected studies

Key points	References	Outcomes	Comments
AVB	Yodogawa *et al*. (28) Takaya *et al*. (42)	High-degree heart block at presentation associated with recovery (p=0.040) and functional responsiveness (p=0.007)	High-degree heart block seem to be associated with recovery and was accessible to treatment
	Kato *et al*. (40)	AVB resolved in 4/7 treated patients versus 0/13 untreated patients (p<0.05)	
VA	Kato *et al*. (40)	Corticosteroid-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*. (27) Naruse *et al*. (43) Segawa *et al*. (44)	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*. (41)	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*. (30)	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.

Appendix 1. Search Strategy

PubMed and Embase :

("sarcoidosis"[MH] OR "besnier boeck schaumann's disease"[TW] OR "benign lymphogranulomatosis"[TW] OR "boeck's disease"[TW] OR "besnier-boeck-schaumann's disease"[TW] OR "besnier-boeck-schaumann syndrome"[TW] OR "besnier boeck schaumann syndrome"[TW] OR "disease schaumann"[TW] OR "besnier-boeck-schaumann disease"[TW] OR "lymphogranulomatosis"[TW] OR "boeck's sarcoid"[TW] OR "boeck disease"[TW] OR "sarcoid reaction"[TW] OR "boecks sarcoidosis"[TW] OR "besnier boeck syndrome"[TW] OR "boeck sarcoid"[TW] OR "boeck; disease"[TW] OR "darier-roussy sarcoid"[TW] OR "besnier boeck disease"[TW] OR "uveoparotid fever"[TW] OR "lymphogranulomatosis; benign"[TW] OR "boeck's sarcoidosis"[TW] OR "besnier boeck schaumann disease"[TW] OR "schaumann syndrome"[TW] OR "lymphogranuloma benignum"[TW] OR "schaumann's disease"[TW] OR "lymphogranulomatosis (benign)"[TW] OR "sarcoidosis"[TW] OR "boeck; sarcoid"[TW] OR "lymphogranulomatosis benign"[TW] OR "benign; lymphogranulomatosis"[TW] OR "schaumann disease"[TW] OR "besnier-boeck disease"[TW] OR "sarcoid boeck"[TW] OR "sarcoid; boeck"[TW] OR "sarcoidoses"[TW] OR "sarcoid"[TW]) AND ("heart"[MH] OR "heart"[TW] OR "hearts"[TW] OR "cardiac"[TW] OR "heart diseases"[MH] OR "cardiac events"[TW] OR "diseases heart"[TW] OR "disease cardiac"[TW] OR "disease;heart"[TW] OR "cardiac disorder"[TW] OR "cardiac diseases"[TW] OR "dysfunction myocardial"[TW] OR "myocardial depression"[TW] OR "diseases of the heart"[TW] OR "disorder of heart"[TW] OR "cardiac event"[TW] OR "dysfunction;heart"[TW] OR "heart disorder"[TW] OR "disease, heart"[TW] OR "dysfunction heart"[TW] OR "heart dysfunction"[TW] OR "diseases, cardiac"[TW] OR "diseases, heart"[TW] OR "dysfunction; myocardial"[TW] OR "disease,

cardiac"[TW] OR "heart diseases"[TW] OR "cardiac disorders"[TW] OR "diseases cardiac"[TW] OR "myocardial dysfunction"[TW] OR "cardiovascular diseases"[TW] OR "morbus; cordis"[TW] OR "heart disorders"[TW] OR "dysfunction; heart"[TW] OR "cardiac therapy"[TW] OR "heart disease"[TW] OR "heart trouble"[TW] OR "cardiac disease"[TW] OR "disease heart"[TW] OR "cardiopathy"[TW] OR "morbus cordis"[TW]) AND ("corticoides"[TW] OR "steroids"[MH] OR "steroids"[TW] OR "steroid"[TW] OR "anti-inflammatory agents"[PA] OR "anti-inflammatory agents"[TW] OR "mineralocorticoids"[MH] OR "glucocorticoids"[PA] OR "glucocorticoids"[TW] OR "mineralocorticoids"[PA] OR "mineralocorticoids"[TW] OR "therapy"[SH] OR "therapeutic use"[SH] OR "pharmacology"[SH] OR "drug therapy"[MH] OR "therapy"[TW] OR "treatment"[TW] OR "therapeutics"[MeSH Terms] OR "therapeutic*"[TW] OR "adrenal cortex hormones"[MH] OR "corticosteroids"[TW] OR "corticoids"[TW] OR "adrenal cortex hormones"[TW] OR "immunosuppressant"[TW] OR "immunosuppressive"[TW] OR "immunosuppressants"[TW] OR "azathioprine"[MH] OR "azathioprine"[TW] OR "imurel"[TW] OR "azothioprine"[TW] OR "prednisone"[TW] OR "prednisone"[MH] OR "prednisolone"[MH] OR "prednisolone"[TW] OR "methotrexate"[MH] OR "methotrexatum"[TW] OR "mexate"[TW] OR "n-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-l-glutamic acid"[TW] OR "methotrexate"[TW] OR "yl5fz2y5u1"[TW] OR "cl 14377"[TW] OR "adverse reaction to methotrexate"[TW] OR "methotrexate sodium"[TW] OR "alpha-methopterin"[TW] OR "sodium methotrexate"[TW] OR "metotrexato"[TW] OR "4-amino-10-methylfolic acid"[TW] OR "mtx - methotrexate"[TW] OR "amethopterin"[TW] OR "59-05-2"[TW] OR "methotrexate hydrate"[TW] OR "methotrexate poisoning"[TW] OR "cyclophosphamide"[MH] OR "cytoxan"[TW] OR "mitoxan"[TW] OR "ciclofosfamide"[TW] OR "neosar"[TW] OR "procytox"[TW] OR "endoxan"[TW] OR "clafen"[TW] OR "cyclophosphamidum"[TW] OR "sendoxan"[TW] OR

"b518"[TW] OR "cyclophosphamide monohydrate"[TW] OR "claphene"[TW] OR "cp monohydrate"[TW] OR "cyclophosphamide anhydrous"[TW] OR "8n3dw7272p"[TW] OR "cpm - cyclophosphamide"[TW] OR "ctx - cyclophosphamide"[TW] OR "cyclophosphanum"[TW] OR "nsc26271"[TW] OR "bis(2-chloroethyl)phosphoramide cyclic propanolamide ester monohydrate"[TW] OR "cytophosphane"[TW] OR "ciclofosfamida"[TW] OR "cyclophosphane"[TW] OR "(-)-cyclophosphamide"[TW] OR "nsc 26271"[TW] OR "revimmune"[TW] OR "b 518"[TW] OR "cyclophosphan"[TW] OR "nsc-26271"[TW] OR "50-18-0"[TW] OR "cyclophosphamide"[TW] OR "b-518"[TW] OR "isofosfamide"[TW] OR "Leflunomide"[MH] OR "leflunomide"[TW] OR "hwa486"[TW] OR "hwa-486"[TW] OR "g162gk9u4w"[TW] OR "Leflunomide"[TW] OR "mycophenolic acid"[MH] OR "hu9dx48n0t"[TW] OR "rs-61443"[TW] OR "cellcept"[TW] OR "mycophenolic acid"[TW] OR "rs61443"[TW] OR "mycophenolic acid morpholinoethyl ester"[TW] OR "acidum mycophenolicum"[TW] OR "sodium salt of mycophenolic acid"[TW] OR "myfortic"[TW] OR "mycophenolate mofetil"[TW] OR "24280-93-1"[TW] OR "sodium mycophenolate"[TW] OR "mycophenolate mofetil hydrochloride"[TW] OR "acide mycophenolique"[TW] OR "acido micofenolico"[TW] OR "mycophenolate"[TW] OR "rs 61443"[TW] OR "chloroquine"[MH] OR "adverse reaction to chloroquine"[TW] OR "886u3h6uff"[TW] OR "chloroquine sulphate"[TW] OR "arechine"[TW] OR "chloroquine measurement"[TW] OR "chloroquine sulfate"[TW] OR "aralen"[TW] OR "chloroquine"[TW] OR "khingamin"[TW] OR "chingamin"[TW] OR "nivaquine"[TW] OR "54-05-7"[TW] OR "chlorochin"[TW] OR "Hydroxychloroquine"[TW])

Supplemental Table 1. Corticosteroids treatment regimen in selected studies

First author	Corticosteroid regimen
Myoren (21)	Prednisolone 30 mg/d for 4 weeks, tapered to 5 - 10 mg over 6 months
Chapelon-Abric (37)	Prednisolone 0,25 - 1,5 mg/kg/d for 6 - 8 weeks, tapered (in case of response) to less than 10 mg/d
Chapelon-Abric (38)	Prednisolone 1 mg/kg/d, tapered (in case of complete or partial response) to less than 10 mg/d over several months
Zhou (30)	Prednisone 20 - 40 mg/d, tapered every 6-8 weeks based on individual response until 5 - 10 mg/d
Orii (39)	Prednisolone 30 mg/d for 4 weeks, tapered to 10 mg/d within 8 weeks, maintenance dose of 10 mg/d
Takaya (19)	Prednisone 30 - 40 mg/d, tapered to 5 - 10 mg/d over a period of 6 to 12 months
Nagai (17)	Prednisolone initial dose was 29,5 ± 4,0 mg, no protocol provided
Nagai (18)	Prednisolone 30 mg/d, tapered to 5 mg/d
Kato (40)	Prednisolone 30 - 40 mg/d, tapered by 5 mg every 4 weeks until a maintenance dose of 4 - 10 mg/d
Padala (27)	Prednisone 30 - 40 mg/d, one month at least, then tapered based on individual responsiveness
Takaya (20)	Prednisone 30 - 40 mg/d, tapered over a period of 6 - 12 months to maintenance dose of 5 - 10 mg/d
Chiu (41)	Prednisolone 60 mg/d for 2 months, tapered gradually to maintenance dose of 10 mg/d
Yazaki (22)	Two groups : high dose (≥40 mg/d, n=30, average dose 54 ± 9 mg/d) and low dose (≤30 mg/d, average dose 29 ± 9 mg/d), tapered to a maintenance dose of 5-15 mg/d
Yodogawa (28)	Prednisone 30 mg/d, tapered over 6 months to maintenance dosage of 5 - 10 mg/d
Takaya (42)	Prednisone 30 - 40 mg/d, tapered over a period of 6-12 months to maintenance dose of 5 - 10 mg/d
Naruse (43)	30 mg/d for 4 weeks, tapered by 5 mg/d every 2 - 4 weeks, until maintenance dose of 5 - 10 mg/d
Yalagudri (11)	Prednisolone 1 mg/kg/d, maximum 60 mg/d, for 8 weeks, tapered over a period of 3 - 4 months before stopping
Segawa (44)	30 mg/d for 4 weeks, tapered by 5 mg/d every 2 weeks, until 20 mg/d during hospitalization, then tapered by 5 mg every 2 - 4 weeks until maintenance dose of 5-10 mg/d
Ballul (10)	Prednisone 60 (20 - 100) mg/d
Nagai (31)	Prednisolone 30 - 60 mg/d as initial dose
Kandolin (45)	Prednisone 0,5- 1 mg/kg/d, tapered over 6 months to 10 - 20 mg/d. Slowly discontinued after 12 months, if LV function was stable

Supplemental Methods 2. SIGN Checklist for Cohort studies

SIGN	METHODOLOGY CHECKLIST 3: COHORT STUDIES

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***
1.1	The study addresses an appropriate and clearly focused question.	Yes □ No □ Can't say □
SELECTION OF SUBJECTS		
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes □ No □ Can't say □ Does not apply □
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes □ No □ Does not apply □
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	Yes □ No □ Can't say □ Does not apply □
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.	

1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes □ No □ Can't say □ Does not apply □
ASSESSMENT		
1.7	The outcomes are clearly defined.	Yes □ No □ Can't say □
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes □ No □ Can't say □ Does not apply □
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Yes □ No □ Can't say □ □
1.10	The method of assessment of exposure is reliable.	Yes □ No □ Can't say □
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes □ No □ Can't say □ Does not apply□
1.12	Exposure level or prognostic factor is assessed more than once.	Yes □ No □ Can't say □ Does not apply □
CONFOUNDING		
1.13	The main potential confounders are identified and taken into account in the design and analysis.	Yes □ No □ Can't say □
STATISTICAL ANALYSIS		
1.14	Have confidence intervals been provided?	Yes □ No □
SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) □ Acceptable (+) □ Unacceptable – reject 0

2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes ☐ Can't say ☐	No ☐
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	Yes □	No □
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.		