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The role of infliximab in treating refractory cardiac sarcoidosis. Case series and systematic review of literature

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Abstract. Cardiac sarcoidosis is associated with significant morbidity and mortality. Immunosuppressive treatment focuses on suppressing myocardial inflammation, which can lead to major adverse events especially when progressing to fibrosis. Conventional management usually includes steroids and steroid sparing agents such as methotrexate and azathioprine. Tumour necrosis factor alpha inhibitors are often reserved for those with a worsening clinical status and/or evidence of persistent inflammatory activity despite conventional therapy. Refractory cardiac sarcoidosis (CS) can be defined as the persistence or progression of active disease, evidenced either by lack of clinical response or persistence or progression of imaging abnormalities, despite being on conventional therapy. In the United Kingdom, tumour necrosis factor alpha inhibitors are currently not licensed for cardiac sarcoidosis as there are no randomised controlled trials to assess the efficacy of infliximab in this patient cohort. In this study, we present the outcomes of six patients treated with infliximab for refractory cardiac sarcoidosis at Royal Brompton Hospital and performed a systematic review of the existing literature on use of infliximab in cardiac sarcoidosis. We searched the Cochrane Library, OVID Medline, OVID Embase, Web of Science and Pubmed to identify 7 full-text studies assessing the role of infliximab in the management of cardiac sarcoidosis. Infliximab was found to play a vital role in stabilising refractory cardiac sarcoidosis by stemming clinical deterioration, arrythmia burden and even reducing steroids requirements. Further prospective trial data is necessary to validate these findings.

Key words: cardiac sarcoidosis, infliximab, tumour necrosis factor

Introduction

Sarcoidosis is an inflammatory granulomatous disease with heterogenous clinical presentations that can affect any organ. Cardiac sarcoidosis (CS) is one form of sarcoidosis associated with diagnostic and therapeutic challenges, and a high morbidity and mortality (1, 2). The original presentation is often variable and ranges from subclinical disease identified in advanced imaging modalities to major arrhythmias, LV dysfunction and even sudden cardiac death (3). Important prognostic factors include the ethnicity, extent and location of myocardial damage, degree of LV dysfunction, and evidence of myocardial inflammatory activity (4-10).

Implantable-cardioverter defibrillators (ICDs) are used for primary or secondary prevention of

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ventricular arrhythmias in CS (11). The role of immunosuppressive treatment in CS focuses on suppressing myocardial inflammation, which could prevent the progression to myocardial fibrosis. Both myocardial inflammation and fibrosis can lead to major adverse events such as life-threatening arrhythmias and heart failure. Corticosteroids and steroid sparing agents such as methotrexate and azathioprine are part of the conventional treatment options used for the management of systemic sarcoidosis, and CS as a result. Corticosteroids are an established traditional treatment option, but often linked with toxicity and long-term side effects. Steroid sparing agents, such as methotrexate and azathioprine, are often used to intensify immunosuppression and allow for safer steroid dose reduction (12-14). Recently, steroid sparing agents have even been considered as induction therapy rather than corticosteroids in some sarcoidosis centres to avoid these side effects (15). Tumour necrosis factor alpha (TNF-a) inhibitors like infliximab are considered a treatment option, likely to be offered to patients with evidence of persistent residual inflammatory activity and /or clinical worsening despite conventional treatment. In this setting, infliximab has demonstrated very good clinical benefit in neurosarcoidosis and lupus pernio (16-18). Similarly, the European Respiratory Society advocate use of infliximab to improve and/or preserve forced vital capacity and quality of life in symptomatic refractory pulmonary sarcoidosis (19, 20).

Emerging data support the use of infliximab in patients with refractory CS (17, 21-26). We present our experience with infliximab in six patients with refractory CS, while performing a systematic review of the current literature in that subject.

Methods

We conducted a review of refractory CS patients who had been or were actively on treatment with infliximab at Royal Brompton Hospital (RBH) from January 2017 to November 2023. A total of six patients were identified. All patients had extra-cardiac sarcoidosis confirmed according to ATR/ERS/WASOG criteria (27). Each case was discussed in our CS multidisciplinary team (MDT) meeting consisting of respiratory physicians with sarcoidosis expertise and cardiologists with specific expertise in sarcoidosis, heart failure, pacing, echocardiography and advanced cardiac imaging (cardiac magnetic resonance (CMR) and fluro-deoxy-glucose positron emission tomography (FDG-PET). A high probability diagnosis of clinical CS was made by the MDT team (Supplementary Figures 1 and 2)(28-31). Refractory CS was defined when patients showed evidence of intolerance to conventional therapies and/or clinical worsening despite conventional treatments for active CS, while there was evidence of persistent or progressive myocardial inflammatory activity on advanced imaging modalities. Serial echocardiographic and FDG-PET scan data after 5 months of infliximab therapy as well as long term clinical data on morbidity and mortality was recorded. All patients were followed up until November 2023. Event data was documented following scrutinization of hospital and general physician records or contact with the referring centre. Given the retrospective nature of our case series review, the institutional research office waived informed patient consent.

We also performed a systematic review to determine the effectiveness and safety profile of infliximab in patients with Cardiac Sarcoidosis and compare the results of our case series. Due to heterogenicity in reporting of interventional outcomes as well as the observational nature of the studies, a meta-analysis was not feasible. Two members of the study team (RA, JO) independently reviewed available literature (Cochrane, PubMed, EMBASE, Web of Science and Medline) and extracted baseline and outcome data from included studies as well as perform risk of bias assessment. Review was conducted according to the PRISMA (Preferred Reporting Items For Systematic Reviews and Meta-analyses) 2020 statement (32).

The search criteria included the terms for population of interest (*cardiac sarcoidosis or sarcoid myocarditis*) and the desired intervention (*infliximab*). Clinical trials, retrospective observational studies and meta-analyses in adults were included in the search criteria. Duplicate publications were excluded, as were review articles, conference papers, case reports and letters. The full search strategy can be found in the Supplement Material (Search Strategy).

Figure 1 illustrates the systematic review process. Studies were considered eligible if they included patients with at least probable diagnosis of cardiac sarcoidosis treated with infliximab according to the Japanese or HRS consensus statement (30, 31). Studies reporting on patients with systemic sarcoidosis that included CS, but lacking sufficient information

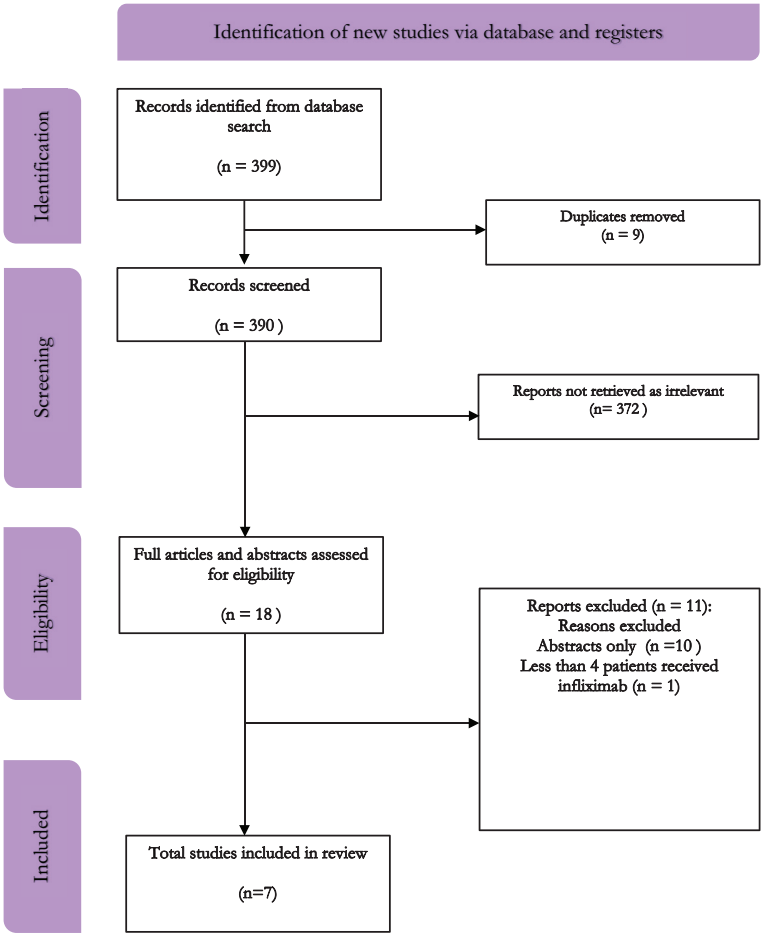

Figure 1. PRISMA tool for identifying studies.

to extract data on the cardiac patients, were excluded. Full articles and case series were included. Case reports were also excluded to limit publication bias. The excluded studies are summarised in Supplement Material **(**Search Strategy**).**

Systematic review data

For this systematic review, reviewers extracted data including: a) study characteristics (author, year of publication, type of study, sample size), b) patient characteristics (age, sex, ethnicity), c) main cardiac manifestations such as presence of atrioventricular block (AVB), ventricular arrhythmias (VA) or heart failure (HF), d) indication for infliximab therapy, e) duration of follow-up and f) outcome measurements in each included study. The outcomes varied in each study and included: major adverse clinical events (defined as cardiac death, ventricular fibrillation, sustained ventricular tachycardia, and hospitalization for heart failure), major adverse drug side effects as well as change in mean prednisolone dose, change in myocardial and extra-cardiac FDG-PET uptake and change in mean left ventricular ejection fraction (LVEF) on imaging. Studies were assessed for risk of bias using the ROBINS-I (Risk Of Bias In Non-randomised Studies of Intervention) tool (33).

Results

Case series

In our case series of 6 CS patients, the median age at CS diagnosis was 46.0 [42-53] years and median duration between CS diagnosis and starting infliximab was 20.5 [7-36] months (Table 1).

Table 1. Demographic details of the six cardiac sarcoidosis patients on infliximab.

	Age at infliximab initiation, Gender	Race	Sarcoidosis disease duration (months)	Biopsy proven extra-cardiac sarcoidosis	Device in situ	Immunosuppression and GDMT	Time from CS diagnosis (months)	Presenting ECG and PVC burden	LVEF	CMR characteristics
Case 1	47, M	Asian	78	Yes – Thoracic lymph node	No	Prednisolone 20mg od, Methotrexate 20mg ow, Hydroxychloroquine 200mg bd	6.5	Sinus rhythm; rare multifocal isolated VEs	58	Subendocardial LGE with active inflammation in mid to apical LV lateral wall
Case 2	48, M	Caucasian	27	Yes – Thoracic lymph node	dc ICD	Prednisolone 10mg od, Methotrexate 15mg ow, Hydroxychloroquine 200mg bd	27	AVB+ VT storm; No PVC	57.5	Active myocardial inflammation at basal septum (RV side) and basal-mid anterior wall
Case 3	43, M	Caucasian	38	Yes – Lungs	No	Prednisolone 20mg od, Methotrexate 15mg ow	38	Sinus rhythm; No PVC	55	Mid-wall fibrosis of basal to mid lateral wall, basal anteroseptum, and mid inferior wall. Linear fibrosis of RV mid-apical inferoseptum
Case 4	54, M	Caucasian	7	No	sc ICD	Prednisolone 20mg, Bisoprolol 5mg bd, Candesartan 24mg od, Spironolactone 12.5mg od	7	VT storm; No PVC	45	Diffuse enhancement of right side of interventricular septum becoming transmural towards apical level and diffuse enhancement in the RV free wall.
Case 5	45, M	Caucasian	36	No	dc ICD	Prednisolone 30mg od, Methotrexate 12.5mg ow, Entresto 97/103mg bd, Eplerenone 25mg od, Bisoprolol 5mg bd	36	Sustained VT initiated by PVC	46	Not available
Case 6	56, M	Caucasian	14	No	dc ICD	Prednisolone 15mg od, Methotrexate 15mg ow	14	AVB; PVC burden 2%	57	LGE in basal anteroseptum (mainly RV) extending anteriorly and focal LGE in the apical lateral wall

AVB= high degree atrio-ventricular block; CS= cardiac sarcoidosis; CMR= cardiac magnetic resonance; dc ICD= dual chamber Implantable Cardioverter Defibrillator; ECG= electrocardiogram; GDMT= Guideline-directed medical therapy for heart failure; M= Male; sc ICD= single chamber Implantable Cardioverter Defibrillator; LGE= late gadolinium enhancement; LV= left ventricular; LVEF= left ventricular ejection fraction; PVC= premature ventricular complex; RV= right ventricular; VEs= ventricular ectopics; VT= ventricular tachycardia

Infliximab was commenced due to persistent inflammation on FDG-PET scan and/or CMR despite being on at least two agents (prednisolone and methotrexate ± hydroxychloroquine) in 5 cases and prednisolone alone (intolerance to methotrexate) in one case. At baseline, three patients presented with ventricular arrhythmias/aborted SCD events, 2 with AVB and 2 with heart failure. After a median follow up of 7.5 [6-10] months of being on infliximab, 6/6 CS patients had decreased myocardial uptake on PET which included complete resolution of FDG-PET signal in one patient (Table 2). All patients were on infliximab from baseline until the end of follow up period (November 2023) apart from one. During a median follow up of 22.5 [18-31] months, one patient (Case 4) died following complications of patent foramen ovale repair. A total of 4/6 patients had an Implantable Cardioverter Defibrillator (ICD) device in situ at the time of infliximab treatment initiation. Case 5 patient received an appropriate anti-tachycardia pacing (ATP) from their ICD 19 months after starting infliximab. They were asymptomatic during this episode. No further events have been noted in Case 5 in the twelve months following this. It is important to note that this patient had a history of VT prior to starting infliximab and had also undergone VT ablation previously. None of the six patients had any premature ventricular complexes (PVCs) during follow-up. During a median follow-up of 7 [6-10] months, there was a significant improvement in serial mean LVEF [53.1±6.0% to 60.7±5.4%, p=0.044]. The two patients (Case 4 and 5) who had heart failure with mildly reduced ejection fraction (HFmrEF) were on guideline directed medical therapy (Table 1). During a median follow-up of 10.5 [9-15] months of being on infliximab treatment, there was a trend in reduction of mean prednisolone dose [19.2±6.6mg to 12.1±7.8mg, p=0.10] (n=6) and a slight increase of mean methotrexate dose [15.5±2.7mg to 18.0±2.7mg, p=0.19] (n=5) whilst there was no change in hydroxychloroquine dose (n=2). None of the patients had a worsening of LVEF or admission with acute heart failure whilst being on infliximab. There were three new cases of infection (1 pneumonia and 2 COVID-19 pneumonitis) and one case of renal cell carcinoma diagnosis three years after infliximab treatment initiation. The drug safety was overall satisfactory since none of the patients required hospitalisation (Table 2). Case 2 patient clinically and radiologically improved after 13 months of treatment and stopped taking infliximab. They were found to have disease relapse (ventricular arrhythmia, FDG-uptake and worsening left ventricular systolic function) seven months after stopping infliximab and were subsequently restarted on infliximab. During a 32 month follow up of being on infliximab again, they demonstrated complete resolution of FDG uptake on subsequent FDG-PET scan and continue to remain clinically asymptomatic.

Table 2. Follow up details of the six cardiac sarcoidosis patients on infliximab.

	Duration of follow up whilst being on infliximab (months)	Change in Prednisolone dose in mg (repeat evaluation*)	Changes to other immunosuppression in mg (repeat evaluation*)	Change in myocardial FDG-PET uptake SUVmax (repeat evaluation*)	Change in extra-cardiac FDG-PET uptake SUVmax (repeat evaluation*)	LVEF change (repeat evaluation*)	Sustained VT	All-cause mortality	Infections
Case 1	63	20 → 20 (8)	MTX 20 → 20 Hydroxychloroquine 200 → 200 (8)	11.1 → 5.1 (6)	18.9 → 3.7 (6)	58 → 64 (5)	0	0	1
Case 2	18	10 → 10 (11)	MTX 15 → 15 Hydroxychloroquine 200 → 200 (11)	10.2 → 2.7 (6)	26 → 6.1 (6)	57.5 → 62 (7)	0	0	1
Case 3	27	20 → 20 (21)	MTX 15 → 15 (21)	11.3 → 3.6 (19)	5.8 → 8.4 (19)	55 → 63 (19)	0	0	1
Case 4	16	20 → 0 (10)	NA	13 → 3.4 (10)	8.8 → 1.0 (10)	45 → 66 (10)	0	1	0
Case 5	31	30 → 15 (9)	MTX 12.5 → 20 (9)	11.3 → 1.0 (9)	14.7 → 4.0 (9)	46 → 51 (7)	1	0	0
Case 6	18	15 → 7.5 (15)	MTX 15 → 20 (15)	14.5 → 5.0 (5)	12.8 → 1.0 (5)	57 → 58 (6)	0	0	0

LVEF=left ventricular ejection fraction; mg=milligrams; MTX= Methotrexate; NA= Not Applicable; SUVmax= Maximum standardized; uptake value; VT= Ventricular tachycardia; * repeat evaluation is in months after starting infliximab

There was also a seventh CS male patient, aged 58, who received infliximab for 5 doses. They had a background of colon cancer, recurrent infections and multi-system sarcoidosis. We did not include this patient in our case series analysis because infliximab treatment here was initiated for refractory neurosarcoidosis. Cardiac involvement was a clinical diagnosis made after the patient had already received a dual-chamber permanent pacemaker for intermittent complete heart block. Indeed, they had no evidence of myocardial oedema on cardiac MRI or FDG-uptake on FDG-PET scan. During a five-month follow-up, the patient's LVEF improved from 58 to 63. Respiratory and neurological symptoms also improved. Infliximab was stopped after the patient presented with chest pain and was given a clinical diagnosis of pericarditis. Given this patient also experienced recurrent hospital admissions with infections, they were not restarted on infliximab again. Notably, hospitalisation due to various infections were very common in this patient before being on infliximab too.

Systematic review

A total of 399 studies met our search criteria. After removing 9 records due to duplicity, 390 publications were screened. A total of 372 were deemed irrelevant because they either did not include cardiac sarcoidosis patients or lacked treatment with infliximab and, 2 were excluded from the final review due to lack of sub-analysis of the CS patients. The main reasons for excluding the remaining publications were lack of relevant information for patients treated with infliximab, abstracts only and case reports format.

Systematic review baseline characteristics

The final 7 studies included a total of 152 CS patients. Table 3 summaries the final studies considered for systematic review (17, 21-26). Across the included studies the age ranged from 20 to 76 years with a male predominance (157/282). The majority of patients were Caucasian (73.3%). Significant

Table 3. Baseline features of studies involving cardiac sarcoidosis patients on infliximab.

First Author, Year	No of patients on IFX n (%)	Male N, (%)	Age Mean ± SD	Caucasian N (%)	Number of regimens used prior to IFX (% of patients)	IFX dose (mg/Kg), frequency	Patients' cardiac manifestations				
							AVB N (%)	VA N (%)	HF N (%)	CS compatible LGE on CMR N (%)	CS compatible FDG-PET uptake N (%)
Churchill, 2023	13/31 (41.9)	21 (68)	52 ± 8	29 (94)	Prednisolone (51.6) At least one steroid-sparing agent (64.5)	6 every 7 weeks	15 (48.4)	14 (45.2)	N/A	N/A	31 (100)
Gilotra, 2021	30/38 (78.9)	22 (58)	49.9 ± 9.5	18 (47)	At least two (94.5)	3-10 every 8 weeks	10 (26.3)	13 (34.2)	13 (34.2)	24/31 (77.4)	32/38 (84.2)
Puyraimond, 2018	19 (100)	13 (68)	Median 39.4 Range: 20-73	10 (53)	At least two (100)	5 every 4-8 weeks	N/A	N/A	N/A	11/15 (73.3)	4/9 (44.4)
Jamilloux, 2017	28 (100)	N/A	N/A	N/A	At least two (95)	3-5 every 4-8 weeks	N/A	N/A	N/A	N/A	N/A
Bakker, 2021	22 (100)	15 (68)	51 ± 10	21 (95.5)	At least two (100)	5 every 4 weeks	7 (31.8)	5 (22.7)	11 (50)*	N/A	20 (90.9)
Stievenart, 2021	4 (100)	4 (100)	40 ± 7.5	4 (100)	At least two (100)	3-5 every 4-8 weeks	0 (0)	0 (0)	2 (50)**	2/4 (50)	2 (50)
Harper, 2019	36 (100)	26 (72)	50 ± 11	28 (78)	At least two (100)	5-10 every 4-8 weeks	7 (19.4)	8 (22.2)	6 (16.7)***	N/A	N/A

*LVEF<50%, **LVEF<40%, ***LVEF<30%; AVB= Atrio-ventricular block; CMR= Cardiac Magnetic Resonance; CS= Cardiac sarcoidosis; FDG-PET=*Fluorodeoxyglucose* (*FDG*)-positron emission tomography; HF= Heart Failure; IFX= Infliximab; LGE= Late-Gadolinium Enhancement; mg/kg=milligrams/kilograms; N= number; N/A= Not Available; SD= Standard deviation; VA= Ventricular arrhythmia

disease activity at baseline as demonstrated by FDG uptake on FDG-PET was reported in 65 patients from 3 reported studies (baseline mean SUVmax 5(26), 3.59 (21) and baseline median SUVmax 5.2 (23). Myocardial damage at baseline defined as late gadolinium enhancement (LGE) on CMR was found in 37/50 (74%) patients from 3 documented studies (21, 22, 24). AVB and VAs prevalence were censored in 5 available studies; (21, 23-26) 30% and 31% respectively (Table 3 and table 4). In 6/7 of the studies, the indication for commencing TNFa therapy is clearly stated to be refractory CS despite 1st, 2nd or even 3rd line immunosuppressive therapy (17, 21-25). Churchill et al report 51.6% of their cohort to be on prednioslone and 64.5% to be on at least one steroid sparing agent before TNFa therapy was commenced(26). Ongoing disease activity on FDG-PET and/or significant arrhythmia and heart failure was felt to represent failure of therapy. The second most common indication was an intolerance to steroids and/or steroid-sparing agents. Diagnosis of cardiac sarcoidosis was confirmed by HRS consensus statement diagnostic criteria(30) in six of the seven studies (17, 21-25), whilst the cohort of patients from Churchill et al (26) also included patients with probable and presumed clinical CS (modified HRS criteria).

Systematic review outcomes

Table 2 and Table 4 details the outcome measures and adverse events for CS patients receiving infliximab. In the seven studies, patients were followed up for a mean of 20.1 months following treatment.

Out of the seven studies, data was available on new device requirement in four studies. From these, one patient received a new CRT device for worsening heart failure (23). From the six studies (n=132) that analysed all-cause mortality in CS patients, overall, all-cause mortality was low at 3.0% after a mean follow up time of 27.0 months. A significantly higher mortality rate was reported in only one study, where 3/19 (15.8%) patients died due to heart failure, lung cancer and respiratory failure from infectious origin (22).

Data on appropriate device therapies was available in four out of the seven studies. In total 7 patients had aborted SCD episodes after commencing infliximab but six out of these seven patients were getting episodes prior to infliximab initiation. Follow up arrhythmia data was available in one study which demonstrated a trend towards elimination of ventricular arrhythmia at 12 months of infliximab use (Ventricular Tachycardia: 3/16 vs 8/25, p=0.07 and Premature Ventricular Complex: 0/16 vs 3/25, p=.0.05) (25). Data on cardiac transplant was recorded in 5 out of the 7 studies (n=113)(21, 23-26). Four patients in total required a cardiac transplant.

FDG-PET outcomes

Three out of seven studies with a total of 58 patients reported serial FDG-PET outcomes as key markers of treatment efficacy (21-23). A total

Table 4. Follow-up data on studies analysing cardiac sarcoidosis patients on infliximab.

First Author, Year	Follow up time (months)	Change in mean prednisolone dose (mean mg, p-value)	Change in FDG-PET uptake (SUVmax, p-value, % responders)	LVEF change (mean, p-value)	Infection rate	Patients discontinuing IFX	Death rate
Churchill, 2023	21.0	-1.7 ± 12.3, p=NS	5 → 4, p=NS, NA	NA	23%	23%	8%
Gilotra, 2021	16.0	21.7 → 7.3, 0.002	3.59 → 0.57, 0.005 73% responders	45% → 47%, 0.10	21%	6.7%	0%
Puyraimond, 2018	36.6	21.4 → 10.9, <0.001	74.7% responders	NA	21%	21%	15.8%
Jamilloux, 2017	NA	23 → 11, 0.001	NA	NA	36%	NA	2.2%
Bakker, 2021	18.9	N/A	5.2 → 2.3, 0.015	45% → 55%, 0.02	9%	13.6%	0%
Stievenart, 2021	54.75	N/A	NA	NA	NA	0%	0%
Harper, 2019	12	20 → 5, <0.001	NA	41% → 42%	13.9%	5.6%	0%

mg=milligrams; FDG-PET= *Fluorodeoxyglucose*-positron emission tomography; IFX= infliximab; LVEF=left ventricular ejection fraction; NA= not available; NS= not significant; SUVmax= Maximum standardised uptake value.

of 38 (65.5%) patients reported at least reduction in FDG uptake, 16 (27.6%) demonstrated stable changes whilst 4 (6.9%) patients had worsening FDG uptake on follow-up. Gilotra et al and Churchill et al described a decrease in the number of LV segments involved following treatment (mean number of segments 3.5 to 1.0, p=0.008; n=16 and mean number of segments 4 to 3, p=NS; n=13)(21, 26). Complete resolution of FDG activity was reported in 53% (16/30) of subjects with interpretable PET scans in the former study (21). Two studies reported a significant reduction in SUVmax post infliximab treatment [3.59±3.70 to 0.57±1.60; p=0.001 (21) and median 5.2 (3.7–8.4) to 2.3 (1.4–2.3), p = 0.02 (23)] whilst one demonstrated a trend towards decrease in mean SUVmax [5±3 to 4±4, p=NS(26)].

Reduction in concomitant immunosuppression

Five studies compared mean or median doses of prednisolone before and after treatment (Table 4). Figure 2 demonstrates the graph for the change in prednisolone dose following treatment with infliximab in the 4 studies that reported the mean doses pre- and post-infliximab. Mean prednisolone dose changed from 21.4±1.1mg to 8.9±2.7mg across these 4 studies (n=116; p<0.01) (17, 21, 22, 25) (Table 4). Churchil et al also reported a non-significant decrease in prednisolone dose (-1.7 ± 12.3mg, n=13)(26). Gilotra et al and Stievenart et al reported that 8/37 (21.6%) patients were completely weaned off prednisolone (21, 24). From available data on individual patients, 11/16 (68.8%) patients from two studies had significant (defined by >5mg) reduction in prednisolone dose (22, 24). In the study by Bakker et al, 5 of the 9 (55.6%) patients were able to reduce

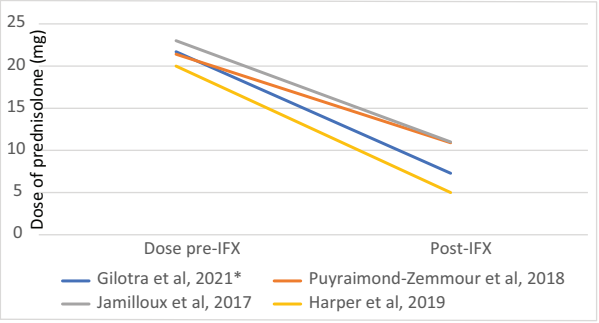

Figure 2. Change in mean Prednisolone dose (mg) following infliximab.

the concomitant immunosuppressive agent from a therapeutic to prophylactic dose (prednisolone <10mg, methotrexate <10mg, azathioprine <100mg, mycophenolate <1000mg) (23). Churchill et al reported outcomes of 31 patients on TNF-a inhibitors (13 infliximab and 15 adalimumab). There was no significant change in steroid-sparing agents doses (methotrexate, leflunomide and mycophenolate) during treatment with these TNF-a inhibitors (26).

Left ventricular function

Figure 3 charts the change in LVEF following treatment with infliximab. Three studies reported mean or median values before and after therapy. The overall LV function appeared to remain stable in all studies, while 1 study reported a statistically significant increase in left ventricular function (23).

In that study a total of 22 patients treated with infliximab demonstrated an increase in median LVEF from 45% to 55% (P= 0.02) over a mean follow-up duration of 19.8 months (23). This increase remained statistically significant after excluding the 3 patients who had heart failure therapy initiated during the study (46.5% to 49.7%, *P*=0.042). Only six (5%) patients in total were found to have worsening heart failure and two patients required hospitalisation for heart failure decompensation while on infliximab treatment. One patient had a 10% decline in LVEF and required heart transplantation, while another one needed a left ventricular assist device while waiting on the transplant list at time of data collection.

Churchill et al reported that mean LVEF decreased before starting TNF-a inhibitors but tended up afterwards, though this increase was not significant (26). One patient (7.7%) was admitted for worsening heart failure, though infliximab had been stopped 22.8 months prior to this. One patient (7.7%) on infliximab required cardiac transplantation but the exact clinical details of this patients are not given (26).

Ventricular arrhythmia and advanced atrioventricular block

Few studies were powered sufficiently to detect significant improvement in the burden of arrhythmia with infliximab and most lacked adequate follow-up time. Only 1 study reported changes in VA burden

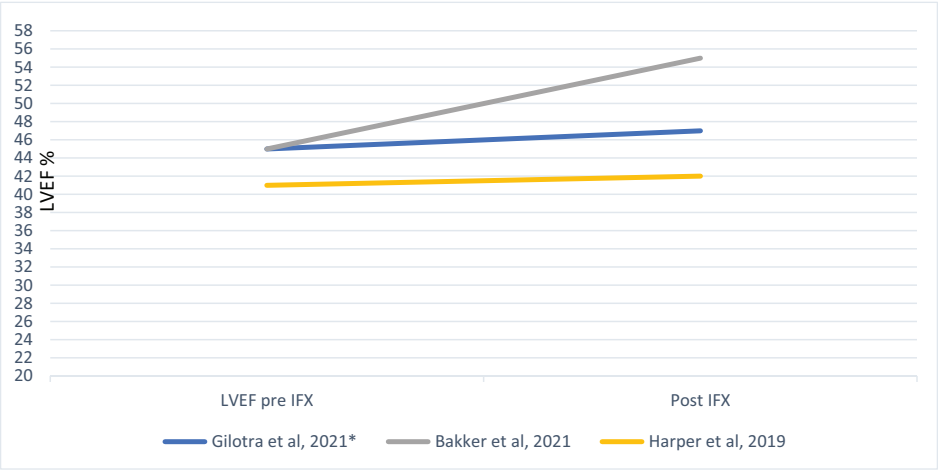

Figure 3. Change in mean LVEF (%) following infliximab.

and showed a reduction in ventricular tachycardia (VT) following therapy (25). In this study of 36 CS patients treated over 12 months with infliximab, a significant reduction in VT (32% to 18.8%, p=0.07) and premature ventricular contractions (PVC) (12% to 0%, p=0.05) was reported (25). There was also a non-significant trend towards a higher burden of non-sustained VT (NSVT) (28% to 40%, p=0.42). Interestingly, there was a non-significant trend towards recovery of atrioventricular nodal function following infliximab treatment ($2^{nd}/3^{rd}$ degree atrioventricular block patients: 2/16 (12.5%) at 12 months vs 7/25 (28%) at baseline (p=0.37) (25).

In another study, 14/31 (45.2%) patients had sustained ventricular tachycardia or ventricular fibrillation as their initial presentation before commencing TNF-a inhibitors (infliximab and adalimumab). It is reported that 2/13 (15.4%) required hospitalisation for ventricular tachycardia after a median follow up of 12.1 months of being on infliximab. Details on VA burden for those not hospitalised is not given (26).

Additional outcome markers of response to therapy

In addition to conventional clinical and imaging biomarkers, two studies assessed response to infliximab therapy with either biomarkers or patient related outcome measures. After 18.9 months of therapy, a significant reduction (15.9%) in serum marker soluble interleukin-2-receptor (s-IL2R) from 3401 to 2432pg/ml, (*P*=0.05) was reported in one study of 22 CS patients. There was also a non-significant improvement in N-terminal pro-brain natriuretic peptide (NT-pro BNP) levels in the same study despite a significant increase in median LVEF (23). Jamilloux et al used the Extrapulmonary Physician Organ Severity Tool (ePOST) to assess response to TNFa treatment in 28 refractory CS patients. The ePOST value reduced significantly from 2.52 to 2.02 (*P*=0.015) (17).

Safety profile of infliximab

The most common adverse effect was infection; reported in all 7 studies. The overall burden was low; 25 infections out of 132 patients (18.9%). 15 (11.4%) patients on infliximab had to prematurely stop treatment due to adverse side effects, infections or fever of unknown aetiology (21-23, 25, 26). The most commonly reported sites of infection were respiratory: 5, shingles: 4, fever of unknown origin: 4, sigmoiditis: 3, pharyngitis: 2, urinary tract infection: 1, intra-abdominal collection: 1, clostridium-difficile: 1 and disseminated cryptococcus: 1.

Discussion

Infliximab is a chimeric monoclonal antibody biologic which acts by binding TNF-a. It is normally used as a third or even fourth line agent in patients with refractory CS (29). Our case series and systematic review of seven retrospective studies suggest that infliximab in refractory CS patients

is a relatively safe 3rd line treatment associated with significant improvement in the level of myocardial inflammation detected by FDG-PET scan, while the concomitant prednisolone treatment was safely reduced. More importantly, changes in core clinical manifestations such as AVB recovery, reduction in VT burden and stability and even improvement in LV function highlight treatment efficacy despite previous intolerance or refractory nature of the disease to conventional therapies. In non-sarcoidosis chronic heart failure patients, TNF-a inhibitors have not shown encouraging results (34). In both our case series and systematic review, a significant minority of patients (5.8%) continued to progress requiring device implantation as prophylaxis, cardiac transplantation or experienced a drop in their LV function. Only 5/138 (3.6%) patients died. One of the patients in our case series experienced relapse of his disease after stopping infliximab for approximately half a year. Although not clearly explored, none of the other seven studies reported a relapse after stopping infliximab. Our experience has shown that careful weaning off infliximab and close monitoring after that is required in all cases.

The infection rate in our cases series and systematic review was 3/6 (50%) and 25/132 (18.9%) respectively. In our case series, given both COVID-19 pneumonitis cases were diagnosed at the peak of pandemic, it is difficult to comment if infliximab was a contributory or protective factor. Indeed, neither of the two cases were severe. Certainly, studies have demonstrated that infliximab may reduce incidence of COVID-19 and facilitate clinical recovery in severe and critical COVID-19 (35, 36). 15 (11.4%) patients from systematic review, and none from our case series, experienced severe infections requiring hospitalization or need for drug withdrawal. These infections had a great range of sites and severity. It is essential that the patients are counselled appropriately about this risk. On a case-by-case basis, antibiotic treatment is recommended after a serious infection and infliximab should be put on hold (37). In our institution, patients are only commenced on infliximab once screening for tuberculosis, human immunodeficiency virus and opportunistic infections are negative as per recommendations from WASOG (38). We would strongly advocate for a multidisciplinary approach in the decision making about use of infliximab. This would improve the selection of patients that would truly benefit from such treatment and avoid major risk associated with infections. In that setting the role of immunologist/infectious disease expert in the multidisciplinary team may be important.

There are some limitations that ought to be pointed out. This case series and systematic review did not focus on TNF-a inhibitors other than infliximab. There is growing evidence that adalimumab leads to clinical benefit with reduction in corticosteroid therapy dose, FDG-uptake and morbidity in refractory cardiac sarcoidosis (26, 39, 40). The studies reviewed here are all retrospective cohort studies, with no randomized controlled clinical trial performed on this topic to date. The lack of control group makes it difficult to be certain that clinical improvement was due to the administration of infliximab as opposed to other factors such as optimisation of heart failure medications and/or cardiac resynchronisation therapy. The concomitant reduction in FDG-PET signal would support the reduction of level of myocardial inflammation even if someone could argue that there can be random fluctuation in FDG-PET signal. Nonetheless, the refractory nature of cases who failed to respond to conventional therapies would increase the risk of life-threatening arrhythmias and sudden cardiac death. Myocardial inflammatory activity is a prognostic factor in cardiac sarcoidosis and should be a regular target of treatment (41). A further bias is publication bias: manuscripts are published if they point to infliximab efficacy, whereas we are not certain about number of patients where infliximab was not beneficial or even was responsible for the death of patients.

There is growing evidence supporting the use of infliximab in refractory CS demonstrated in both clinical, functional and tissue characterization parameters. However, infliximab may be associated with risk of infections and each case should be dealt with on an individual basis after review of all information by an experienced multidisciplinary team. Further prospective randomized controlled clinical trial data with adequate power is necessary to validate these findings.

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Conflict of Interest: None

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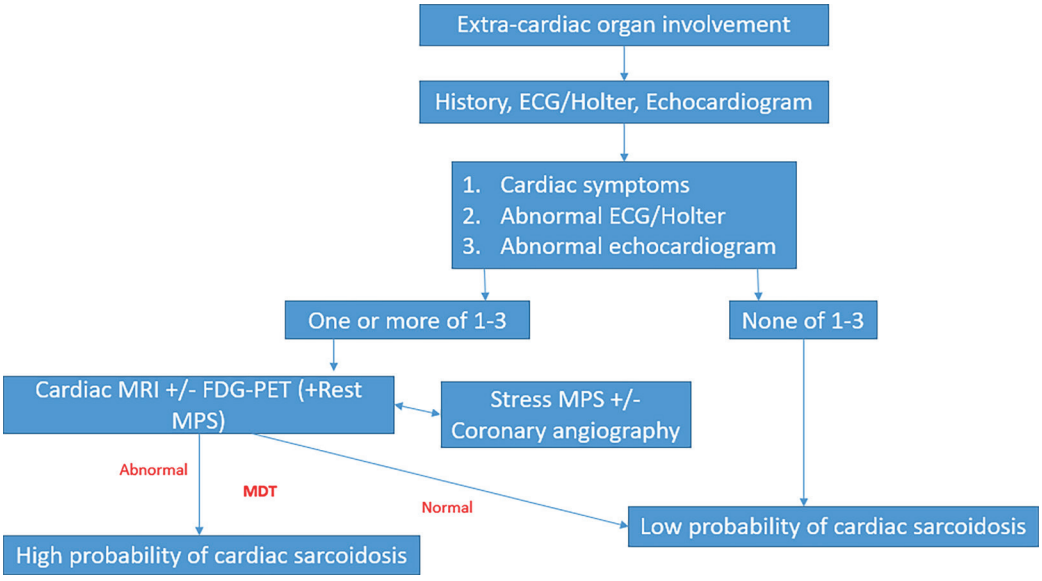
Supplement material

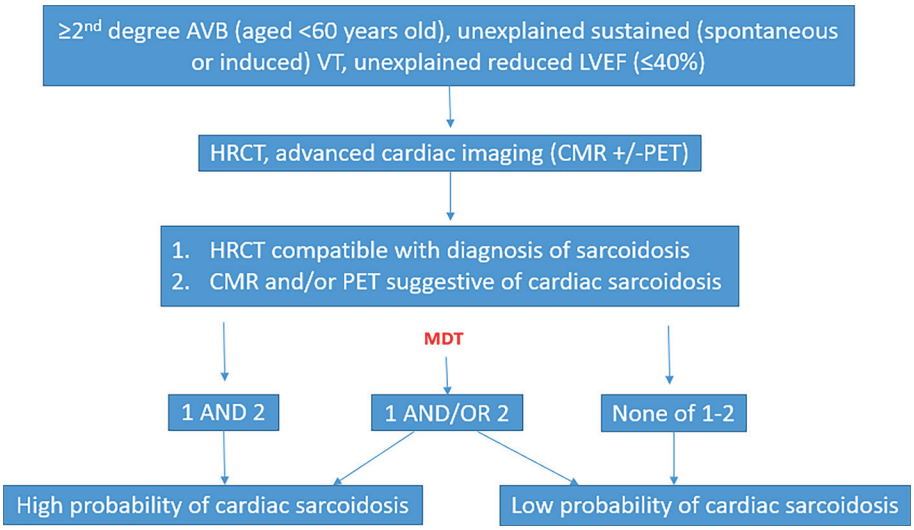
Systematic review search strategy

Once a systematic search strategy was agreed, 4 major databases were searched (Pubmed, Cochrane, EMBASE, Web of Science and Medline) from inception of database to current day. The final searches were performed on 30th November 2023. The search criteria included the terms for population of interest (*cardiac sarcoidosis or sarcoid myocarditis*) and the desired intervention (*infliximab*). The search was not limited by language. Clinical trials, retrospective observational studies, meta-analyses and observational studies in adults >18 years were included in the search criteria. The papers searched were all added to Covidence and duplicates were removed. Abstract publications were searched separately for full-text papers and if full-text was published, it was included in the systematic review. The review was not registered and formal protocol not prepared.

Supplementary Figure 1 and 2 illustrates the screening process. Studies were deemed eligible if they included patients diagnosed as having cardiac sarcoidosis being treated with infliximab. The diagnosis of CS was based on indicative imaging and/or clinical findings. Studies whereby patients in the cohort were treated with another TNFa were also included if infliximab was one of the agents. Studies reporting on patients with systemic sarcoidosis that



Supplement Figure 1. The Royal Brompton Hospital Diagnostic Protocol for clinical diagnosis of cardiac sarcoidosis in presence of extra-cardiac involvement (adapted from Japanese, HRS and WASOG Sarcoidosis Organ Assessment Criteria (1-4)). ECG= Electrocardiogram; Cardiac MRI= Cardiac Magnetic Resonance Imaging; FDG-PET= fluoro-deoxy-glucose positron emission tomography; HRS= Heart Rhythm Society; MDT= multidisciplinary team; MPS= myocardial perfusion scan; WASOG= World Association of Sarcoidosis and other Granulomatous Disorders.



Supplement Figure 2. The Royal Brompton Hospital Diagnostic Protocol for presumed clinical diagnosis of cardiac sarcoidosis in absence of extra-cardiac involvement (adapted from Japanese, HRS and WASOG Sarcoidosis Organ Assessment Criteria (1-4)). AVB= Atrioventricular block; CMR= Cardiac Magnetic Resonance; FDG-PET= fluoro-deoxy-glucose positron emission tomography; HRCT= High Resolution Computed Tomography; HRS= Heart Rhythm Society; LVEF= Left ventricular ejection fraction; MDT= multidisciplinary team; MPS= myocardial perfusion scan; VT= Ventricular tachycardia; WASOG= World Association of Sarcoidosis and other Granulomatous Disorders

included CS, but lacking sufficient information to extract data on the cardiac patients, were excluded. Only studies that had published full articles involving four or more patients treated with infliximab were included. Case reports involving less than 4 patients were excluded to reduce the risk of reporting bias.

The following 10 studies were considered but after reading the abstracts excluded due to no full text available (Kandolin et al, 2017; Cundiff et al, 2019; Baker et al, 2019; Kowlgi et al, 2019; Gilotra et al, 2020; Baker at al, 2020; Pillarisetty et al, 2019; Sinokrot et al. 2019; Kowlgi et al, 2017; Devraj et al, 2020). These were conference abstracts only.

One study (Pillarisetty et al, 2019) was exclude as less than 4 patients in the treatment group received infliximab.

Approximately, 25 (91%) of the CS patients in the study by Jamilloux et al received Infliximab (5). In their 2017 study, as a proportion, 6%, 3% and 0.7% were treated with adalimumab, etanercept and certolizumab respectively. 8 patients in the study by Gilotra et al received adalimumab instead of infliximab (6). Similarly, 18 patients in the study by Churchill et al received adalimumab (7).

Supplementary material references

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