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## TOPICS IN REVIEW

# Narrative review of adalimumab for the treatment of cardiac sarcoidosis

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Cardiac sarcoidosis (CS) remains the second leading cause of death in patients with sarcoidosis, primarily because of its association with heart failure and arrhythmias. While corticosteroids are first-line therapy, their long-term use in CS is associated with serious adverse events, necessitating alternative immunosuppressive therapies, such as tumor necrosis factor inhibitors. Although infliximab is the most studied tumor necrosis factor inhibitor for refractory CS, adalimumab has emerged as a potential alternative. To that end, we reviewed the literature on adalimumab treatment in CS, identifying 12 publications published between January 2000 and September 2024 encompassing 240 patients, of whom 100 (42%) received adalimumab and were followed for at least 6 months. Most patients demonstrated stable or improved left ventricular ejection fraction, even those with initially low left ventricular ejection fraction and reduced cardiac <sup>18</sup>F-fluorodeoxyglucose uptake on positron emission tomography-computed tomography. Adalimumab was generally well-tolerated with few reported infections or adverse events.

However, these findings are limited by significant heterogeneity in study design, variability in patient populations, and a lack of standardized outcome measures, which restrict their generalizability. While adalimumab shows promise as a therapeutic option for refractory CS, robust, multicenter, randomized controlled trials are needed to validate these findings and define adalimumab's role in clinical practice.

**KEYWORDS** Adalimumab; Arrhythmias; Cardiac sarcoidosis; Fully human monoclonal antibody; Granulomatous inflammation; Heart failure; Tumor necrosis factor

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## Introduction

Cardiac sarcoidosis (CS) is a potentially life-threatening manifestation of sarcoidosis, characterized by granulomatous inflammation within the myocardium. Although sarcoidosis primarily affects the lungs and lymph nodes, cardiac involvement can lead to severe outcomes, including heart failure, arrhythmias, and sudden cardiac death.<sup>1</sup> Diagnosis and management of CS remain challenging because of the heterogeneity of clinical presentations, ranging from asymptomatic cases to life-threatening conditions. Standard treatment often involves corticosteroids as first-line therapy. However, their long-term use is associated with significant adverse events, leading to an increased interest in corticosteroid-sparing agents.

Tumor necrosis factor (TNF) plays a crucial role in sarcoidosis by driving granuloma formation through its production by immune and nonimmune cells.<sup>2–4</sup> Evidence from studies has revealed that patients with sarcoidosis exhibit increased TNF activity compared with healthy individuals,<sup>5</sup> with specific genetic factors, such as the TNF- $\alpha$ -308 polymorphism, influencing susceptibility and response to TNF inhibitors such as adalimumab (ADA) and infliximab (IFX).<sup>6</sup> TNF inhibitors have emerged as potential therapeutic options in sarcoidosis, particularly in refractory cases or when corticosteroids or other corticosteroid-sparing agents are contraindicated or poorly tolerated.<sup>7,8</sup> IFX has been the most widely studied TNF inhibitor in sarcoidosis and is often considered the preferred biologic agent (by default), as supported by 2 recent clinical/scientific consensus statements for the diagnosis and management of CS, published by the European Society of Cardiology (ESC)<sup>9</sup> and the American Heart Association.<sup>10</sup> However, ADA, which was not discussed in the ESC consensus statement, may serve as a valuable alternative to IFX in the treatment of CS for several

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## KEY FINDINGS

- We reviewed the literature on adalimumab treatment in cardiac sarcoidosis, identifying 12 publications between January 2000 and September 2024.
- The 12 publications spanned 240 patients, of whom 100 (42%) received adalimumab and were followed for at least 6 months.
- Most patients demonstrated stable or improved left ventricular ejection fraction (LVEF), including those with initially low LVEF, and reduced cardiac <sup>18</sup>F-fluorodeoxyglucose uptake on positron emission tomography-computed tomography.
- Adalimumab was generally well-tolerated with few reported infections or adverse events.
- Adalimumab is a promising option for refractory cardiac sarcoidosis. Randomized controlled trials are needed to validate these findings and define adalimumab's role in clinical practice.

reasons. These include differences in its immunogenicity related to its molecular structure (Figure 1), ease of administration (subcutaneous vs intravenous), and patient-specific factors. By its route of administration, ADA also offers the convenience of self-administration at home, reducing the need for hospital visits, which can improve health-related quality of life for patients with limited access to infusion centers or those seeking more flexibility in their treatment regimen. In other autoimmune diseases, such as rheumatoid arthritis and inflammatory bowel disease, ADA has been widely adopted as a result of these factors, with its use supported further by comparable efficacy profiles observed in meta-analyses<sup>11,12</sup> and cohort studies.<sup>13</sup> Conversely, IFX has been associated with a greater risk of adverse events, as evidenced by a meta-analysis demonstrating significantly increased risk for patients with Crohn's disease.<sup>14</sup>

Accordingly, this narrative review aims to evaluate the efficacy and safety of ADA in patients with CS, particularly in patients with heart failure. By synthesizing data from the current literature, we seek to provide a comprehensive

overview of ADA's potential role as a targeted therapy for patients with CS.

## Methods

The authors conducted a narrative review to comprehensively examine ADA's efficacy and safety in treating CS. Given the limited but growing body of literature, and owing to the heterogeneity of study designs and small sample sizes, including retrospective observational studies, case series, and case reports, a systematic review or meta-analysis was not feasible.

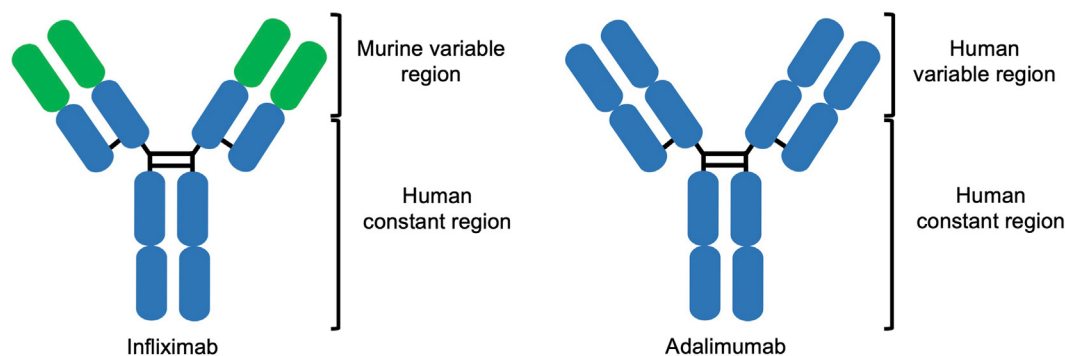
To gather the relevant studies, we searched across several databases, including Medline, Embase, Cochrane Library, and Web of Science. The search focused on studies published between January 2000 and September 2024, using the key words "cardiac sarcoidosis" or "sarcoid myocarditis," and "adalimumab." Clinical trials, retrospective observational studies, case series, and case reports were included. Studies were excluded if they were posters, studies with only abstracts available, studies that described the use of ADA without reporting treatment outcomes, or studies with a mean or median follow-up of <6 months after ADA initiation.

The statistical analyses performed in this review included a paired *t* test used to compare left ventricular ejection fraction (LVEF) before and after the initiation of TNF inhibitors and a  $\chi^2$  test to compare infection rates between ADA and IFX. In addition, data extraction from figures in the reviewed publications was facilitated using WebPlotDigitizer free software (<https://automeris.io/>).

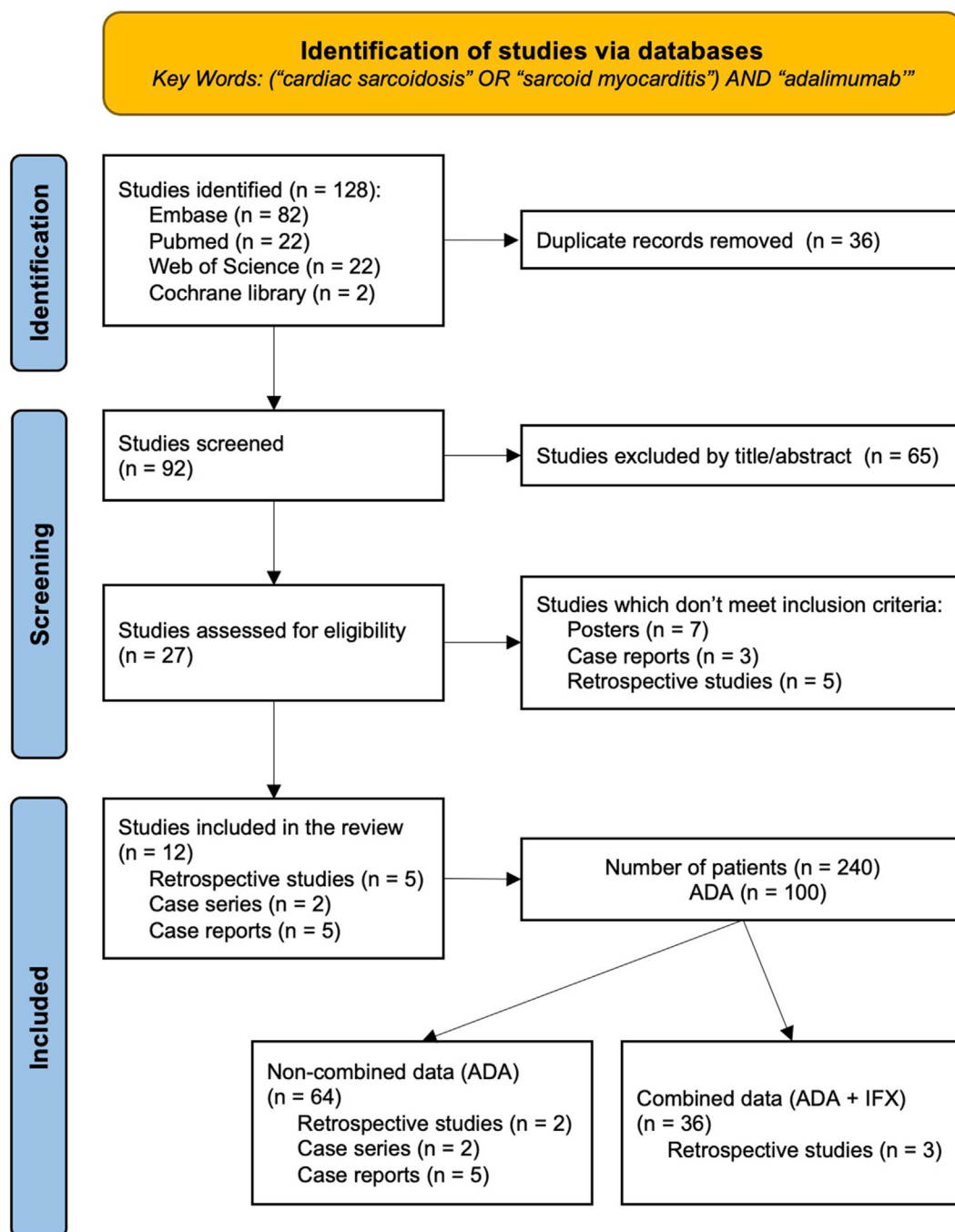
## Results

### Demographic and clinical characteristics

A total of 128 publications were identified across all databases. After removing duplicates and performing a manual screening, 12 publications from 2018 to 2024 were included in this review, as summarized in a Consolidated Standards of Reporting Trials (CONSORT) diagram (Figure 2). These consisted of 5 retrospective observational studies (one of which was a multicenter study),<sup>15–19</sup> 2 case series,<sup>20,21</sup> and 5 case reports.<sup>22–26</sup> Together, these papers included a total of 240 patients (mean age 52.3 years; 58.6% male), of whom 156 (65%) received a TNF inhibitor (ADA or IFX),



**Figure 1** Schematic comparative structure of infliximab and adalimumab.



**Figure 2** CONSORT diagram. ADA = adalimumab; CONSORT = Consolidated Standards of Reporting Trials; IFX = infliximab.

with 100 (41.7%) receiving ADA, the population of interest in our present study. At least 181 (75.4%) patients fulfilled the Japanese Circulation Society diagnostic criteria<sup>27</sup> for CS (either histological or clinical). The remaining 59 (24.6%) patients were classified as possible or presumed CS, with 43 (17.9%) lacking biopsy-proven cardiac or extracardiac involvement. Of these 43 patients with suspected isolated CS, 7 (16.3%) were treated with ADA. These patients were classified as possible/presumed CS if imaging findings on <sup>18</sup>F-fluorodeoxyglucose positron emission

tomography-computed tomography (<sup>18</sup>F-FDG PET-CT) or cardiovascular magnetic resonance were highly suggestive of CS and met at least one of the following secondary criteria: corticosteroid-responsive cardiomyopathy or heart block, unexplained LVEF <40%, unexplained sustained ventricular tachycardia, Mobitz type II second- or third-degree atrioventricular block (AVB), and the exclusion of other causes (Table 1).

Of the 100 patients receiving ADA, 52 (52%) received 40 mg every other week, 15 (15%) received 40 mg weekly, and

**Table 1** Demographic characteristics, clinical characteristics, and cardiac sarcoidosis diagnostic criteria

Study	Year	Country	Study type	Sample size, n	No. of patients receiving ADA (%)	No. of patients receiving IFX (%)	Age (y), mean ( $\pm$ SD or range)	Sex: M/F, n (%)	Race: white, n (%)	Modified 2014 HRS diagnostic criteria, n (%; ADA = n)	2016 JCS diagnostic criteria (histological or clinical) fulfilled, n (%)
<i>Retrospective observational studies</i>											
Baker et al <sup>15</sup>	2020	United States	Retrospective single-center	77 (100%)	10 (13%)	10 (13%)	55 $\pm$ 7	M, 47 (61%)	W, 51 (66%)	Definite: 11 (14%; ADA = 2) Probable: 31 (40%; ADA = 6) Possible: 35 (46%; ADA = 2)	NA
Frischknecht et al <sup>16</sup>	2023	Switzerland	Retrospective single-center	50 (100%)	First F-U: 10 (20%) Last F-U: 31 (62%)	First F-U: 1 (2%) Last F-U: NA	51.3 $\pm$ 11.4	M, 26 (52%)	NA	NA	34 (68%) (the other 16 patients: histological ECS with typical cardiac FDG PET-CT findings)
Gilotra et al <sup>17</sup>	2021	United States	Retrospective multicenter	38 (100%)	8 (21%)	30 (79%)	49.9 $\pm$ 9.5	M, 22 (58%)	W, 18 (47%)	NA	38 (100%)
Churchill et al <sup>18</sup>	2023	United States	Retrospective single-center	31 (100%)	18 (58%)	13 (42%)	52 $\pm$ 8	M, 21 (68%)	W, 29 (94%)	Definite: 3 (10%; ADA = 2) Probable: 20 (64%; ADA = 11) Possible: 8 (26%; ADA = 5)	NA
Rosenthal et al <sup>19</sup>	2019	United States	Retrospective single-center	28 (100%)	19 (68%)	0 (0%)	52.2	M, 16 (57%)	NA	NA	28 (100%)
<i>Case series</i>											
Sweis et al <sup>20</sup>	2022	United States	Case series	7 (100%)	7 (100%)	0 (0%)	61.3 (54–73)	M, 2 (29%)	W, 7 (100%)	NA	7 (100%)
Stievenart et al <sup>21</sup>	2021	France	Case series	4 (100%)	2 (50%)	2 (50%)	34, 36, 38, 53	M, 4 (100%)	W, 4 (100%)	NA	4 (100%)
<i>Case reports</i>											
Saab et al <sup>22</sup>	2018	United States	Case report	1	1	0	33	M	W	NA	1
Theodore et al <sup>23</sup>	2019	India	Case report	1	1	0	35	F	NA	NA	1
Krishnan et al <sup>24</sup>	2020	United States	Case report	1	1	0	41	F	NA	NA	1
Li et al <sup>25</sup>	2022	China	Case report	1	1	0	45	M	NA	NA	1
Vasquez and Andrade-Bucknor <sup>26</sup>	2024	United States	Case report	1	1	0	54	F	NA	NA	1

ADA = adalimumab; ECS = extracardiac sarcoidosis; F = female; FDG = fluorodeoxyglucose; F-U = follow-up; IFX = infliximab; JCS = Japanese Circulation Society; M = male; NA = not available; PET-CT = positron emission tomography-computed tomography; W = white.



the dosage for the remaining 33 (33%) was not reported (usual therapeutic ranges: from 40 mg every other week to 40 mg weekly). Both ADA and IFX were predominantly used for refractory cases, defined by persistent or worsening cardiac  $^{18}\text{F}$ -FDG uptake on PET-CT or by relapsing/worsening cardiac manifestations. In 4 of the 5 retrospective studies and the 2 case series, the mean or median follow-up after ADA initiation ranged from at least 12 to 32.7 months. For case reports, it ranged from 8 to 24 months (Table 2). At the time of ADA initiation ( $n=33$ ), 31 (94%) patients were receiving prednisone and all were receiving a nonbiologic disease-modifying antirheumatic drug (DMARD), with methotrexate being the most frequently used agent (94%). In studies including both IFX and ADA data ( $n=89$ ), 68 (76%) patients were treated with prednisone and 75 (84%) received a nonbiologic DMARD. Of the 75 patients, 44 (59%) were also receiving methotrexate (Online Supplemental Table 1). Cardiac manifestations predominantly included high-grade AVB, ventricular arrhythmias, and heart failure, as summarized in Table 2.

## Outcomes

### *Adalimumab efficacy*

Three of the 5 retrospective studies<sup>15,17,18</sup> that included both ADA and IFX did not report specific end points for ADA separately, but instead combined the outcomes for both treatments. One study included 10 patients treated with each medication,<sup>15</sup> another reported 18 and 13 patients, respectively,<sup>18</sup> and the last study included 8 patients treated with ADA and 30 with IFX,<sup>17</sup> totaling 36 patients treated with ADA and 53 with IFX. The remaining publications focused exclusively on ADA.

The study endpoints regarding the efficacy of ADA and ADA/IFX were not standardized across the studies. However, they can broadly be grouped into 4 main categories:

1. LVEF: before vs after ADA initiation
2.  $^{18}\text{F}$ -FDG uptake: partial or complete resolution, reduction in cardiac metabolic activity, maximum standardized uptake value, or number of left ventricular segments involved
3. Ventricular arrhythmia and high-grade AVB: before vs after ADA initiation
4. Prednisone dosage: reduction or discontinuation after ADA initiation

All endpoints are summarized in Table 3 (focused on ADA) and Table 4 (including ADA/IFX combined data).

### *LVEF*

In the ADA-focused study, which included 42 patients (9 [21%] with LVEF  $\leq 35\%$  before ADA initiation), all patients experienced stable or improved LVEF. In the study by Frischknecht et al<sup>16</sup> ( $n=31$ ), the mean LVEF increased significantly from 51% to 53% ( $P = .012$ ). When data from case series and case reports were combined ( $n=11$ ), a

significant improvement in LVEF was observed after ADA initiation ( $42\% \pm 13.9\%$  vs  $48.9\% \pm 8.2\%$ ;  $P = .036$ ). However, data from Frischknecht et al could not be included in this combined analysis because of the absence of SD values.

In the 3 studies combining data for ADA and IFX, which included 89 patients (17 [19%] with LVEF  $\leq 35\%$ ), LVEF remained predominantly stable. Only 1 of 38 (2.6%) patients in a retrospective study experienced a significant decrease (defined in that study as a  $\geq 10\%$  reduction), from 35% to 20% during follow-up.<sup>17</sup> Another study reported that only 1 of 31 (3.2%) patients had LVEF  $< 30\%$  after TNF-inhibitor initiation, with all other patients showing stable or improved LVEF.<sup>18</sup> Owing to insufficient statistical data in the study by Churchill et al,<sup>18</sup> we were unable to combine results from all 3 studies. However, pooling data from Gilotra et al<sup>17</sup> and Baker et al<sup>15</sup> revealed a significant improvement in LVEF ( $44.4\% \pm 15.5\%$  vs  $46.8\% \pm 14.8\%$ ; mean difference 2.40; 95% confidence interval [CI] 0.24–4.55;  $P=.03$ ). Figure 3A provides a summary of LVEF outcomes for both the ADA and ADA/IFX groups.

### *$^{18}\text{F}$ -FDG PET-CT follow-up*

In the ADA-focused study, which included 60 patients, 46 (76.6%) had complete resolution of  $^{18}\text{F}$ -FDG uptake and 6 (10%) had partial resolution. One study demonstrated a significant reduction in cardiac metabolic activity after ADA initiation ( $437 \pm 344$  to  $125 \pm 158$ ;  $P = .026$ ).<sup>9</sup> For the ADA/IFX combined data, Gilotra et al<sup>17</sup> reported 22 (73%) patients with complete or partial resolution of  $^{18}\text{F}$ -FDG uptake and a substantial reduction in involved segments and maximum standardized uptake value. Another study also noted a significant reduction in involved segments, noting that both ADA and IFX contributed to this reduction.<sup>18</sup> Finally, a third study reported complete resolution of  $^{18}\text{F}$ -FDG uptake in 100% of patients treated with ADA or IFX.<sup>15</sup>

### *Ventricular arrhythmias and high-grade AVB*

Data on ventricular arrhythmia outcomes, despite their significant impact on morbidity and mortality, remain sparse and fragmented in the reviewed publications. Notably, 1 retrospective study reported no recurrent ventricular tachycardia or new-onset AVB in 19 (100%) patients treated with ADA.<sup>19</sup> Two case reports documented improvement in ventricular tachycardia,<sup>23,25</sup> with 1 also exhibiting resolution of third-degree AVB.<sup>25</sup> For combined ADA/IFX data, 1 study reported a reduction in ventricular arrhythmias after TNF-inhibitor initiation (13 [34%] patients vs 3 [8%] patients), although none of the 5 patients with third-degree AVB showed resolution.<sup>17</sup>

### *Prednisone dosage reduction or discontinuation*

One study reported a trend toward lower prednisone dosages in patients treated with ADA than in those treated with azathioprine ( $7.3 \pm 5.1$  mg/d vs  $9.9 \pm 5.2$  mg/d, respectively;  $P > .05$ ).<sup>16</sup> In a case series of 7 patients, 2 (29%) reduced their prednisone dosages (from 7.5 to 1.25 mg/d and from 8.75 to 2 mg/d) and 5 (71%) discontinued prednisone.<sup>20</sup>

**Table 2** Baseline characteristics and immunosuppressive therapy

Study	No. of patients receiving TNFi (IFX + ADA) (% of the total cohort)	No. of patients receiving ADA (%; dosage)	TNFi follow-up (mo), mean $\pm$ SD or (range), median (IQR), or no.	Cardiac manifestations, n (%)	Concomitant drugs at TNFi initiation, n (%)	Reasons for TNFi initiation, n (%)
<i>Retrospective observational studies</i>						
Baker et al <sup>15*</sup>	20 (26%)	10 (50%; NA)	12 (at least)	Third-grade AVB 7 (35%), VA + AA 11 (55%), HF 3 (15%)	PDN 13 (65%), MTX 20 (100%)	Persistent cardiac <sup>18</sup> F-FDG uptake, worsening of HF, or arrhythmia burden: 17 (85%)
Frischknecht et al <sup>16†</sup>	First follow-up: 11 (22%) Last follow-up: NA	First follow-up: 10 (20%; 9 on 40 mg/wk) Second follow-up: 15 (30%; NA) Last follow-up: 31 (62%; NA)	13.6 $\pm$ 9.2	High-grade AVB 19 (38%), sVT + VF 12 (24%), HF (NA)	PDN (NA), AZA (NA), MTX (NA), MMF (NA), other DMARDs (NA)	First-line (open to physician choice): 10 (32%) Insufficient therapy response: 16 (52%) Adverse events of immunosuppressors: 5 (16%)
Gilotra et al <sup>17*</sup>	38 (100%)	8 (21%; 40 mg/2 wk)	16.2 (13.5)	Third-degree AVB 5 (13%), VA 13 (34%), Afib 4 (11%), HF 13 (34%)	PDN 33 (87%), AZA 8 (21%), MTX 11 (29%), MMF 16 (42%)	Persistent cardiac <sup>18</sup> F-FDG uptake: 22 (58%) Cardiac events: 13 (34%) Intolerance to other regimen: 17 (45%)
Churchill et al <sup>18*</sup>	31 (100%)	18 (58%; 40 mg/2 wk)	13 (12–19) <sup>†</sup>	Third-degree AVB 13 (42%), PVCs >1% 13 (42%), nsVT 13 (42%), sVT + VF 14 (45%), HF NA	PDN 22 (71%), MTX 13 (42%), leflunomide 3 (10%), MMF 4 (13%), rituximab 2 (6%)	Mainly insufficient therapy response or intolerance to other regimens
Rosenthal et al <sup>19‡</sup>	19 (68%)	19 (68%; 40 mg/2 wk)	NA (total CS follow-up: 49 $\pm$ 18)	High-grade AVB 11 (39%), PVCs >1% 16 (57%), nsVT 10 (36%), sVT/VF 18 (64%), HF 11 (39%)	PDN 19 (100%), MTX 19 (100%)	Persistent cardiac <sup>18</sup> F-FDG uptake or intolerance to MTX
<i>Case series<sup>†</sup></i>						
Sweis et al <sup>20</sup>	7 (100%)	7 (100%; 5 on 40 mg/wk)	32.7 (15–82)	High-grade AVB 3 (43%), VA 3 (43%), HF 3 (43%)	PDN 7 (100%), MTX 7 (100%), MMF 1 (14%)	Insufficient therapy response: 6 (86%)
Stievenart et al <sup>21</sup>	4 (100%)	2 (50%; 40 mg/2 wk)	14, 13	PVCs >1% 1 (50%), HF 1 (50%)	MTX 2 (100%)	Relapse on MTX: 2 (100%)
<i>Case reports<sup>‡</sup></i>						
Saab et al <sup>22</sup>	1	1 (NA)	24	Mobitz type II second-degree AVB	PDN, MTX	Relapse on MTX
Theodore et al <sup>23</sup>	1	1 (40 mg/2 wk)	14	sVT, HF	PDN, MTX	Persistent arrhythmia under high dosage of PDN and of MTX

Krishnan et al <sup>24</sup>	1	1 (NA)	24	HF	PDN, AZA	Persistent cardiac <sup>18</sup> F-FDG uptake + worsening of HF
Li et al <sup>25</sup>	1	1 (40 mg/2 wk)	8	Third-degree AVB, PVCs >1%, nsVT, atrial flutter, Afib	PDN, MMF	Persistent arrhythmia under high dosage of PDN and of MMF (2 g/d)
Vasquez and Andrade-Bucknor <sup>26</sup>	1	1 (40 mg/wk)	21	RBBB, HF	PDN, MTX	First intention because of severe heart involvement

AA = atrial arrhythmia; ADA = adalimumab; Afib = atrial fibrillation; AVB = atrioventricular block; AZA = azathioprine; CS = cardiac sarcoidosis; DMARD = disease-modifying antirheumatic drug; FDG = fluorodeoxyglucose; HF = heart failure; IFX = infliximab; IQR = interquartile range; MMF = mycophenolate mofetil; MTX = methotrexate; NA = not available; nsVT = nonsustained ventricular tachycardia; PDN = prednisone; PVC = premature ventricular contraction; RBBB = right bundle branch block; sVT = sustained ventricular tachycardia; TNFi = tumor necrosis factor inhibitor; VA = ventricular arrhythmia; VF = ventricular fibrillation.

\*Studies including both ADA and IFX.

<sup>†</sup>Data from studies including both ADA and IFX that specifically focused on ADA.

<sup>‡</sup>Studies specifically focused on patients treated with ADA.

Three case reports further highlighted this outcome, with 2 reporting prednisone discontinuation<sup>22,26</sup> and 1 documenting a reduction from >40 to 15 mg/d.<sup>25</sup>

For combined ADA/IFX data, 2 studies reported reductions in prednisone dosage after TNF-inhibitor initiation,<sup>17,18</sup> with 1 exhibiting a trend toward greater reduction in patients treated with ADA than with IFX ( $-4.7 \pm 7.7$  vs  $-1.7 \pm 12.3$ , respectively;  $P = .052$ ).<sup>18</sup> Another study noted a substantial reduction, from 23 to 4 mg/d, within 6 months of TNF-inhibitor therapy, though without a reported  $P$  value.<sup>15</sup> Pooling these data was not possible because of heterogeneity in outcomes. Figure 3B summarizes all the ADA and ADA/IFX data.

### Cardiac relapse with TNF inhibitors

No published studies evaluated long-term outcomes, including relapse rate of patients with CS treated with TNF inhibitors. Rosenthal et al<sup>19</sup> reported no radiologic relapses in 19 patients treated with ADA compared with 4 relapses in 25 patients treated with methotrexate (20 mg/wk) and 8 relapses in 9 patients who discontinued immunosuppressive therapy. However, follow-up for patients on ADA was shorter than that for those on methotrexate, as methotrexate was used as a first- or second-line treatment while ADA was administered as a third-line therapy.

### Safety

In 100 patients treated with ADA, 4 infections were reported for a total of 4 (4%) patients, including 1 *Mycobacterium avium* complex infection, 1 unspecified lung infection, 1 cellulitis, and 1 unspecified infection, all leading to temporary treatment discontinuation. Permanent discontinuation occurred in 4 (4%) patients, 1 due to aseptic meningitis and 3 due to noninfectious adverse events. One death, attributed to a stroke, was recorded during the follow-up period (Table 3). In 56 patients treated with IFX, 12 infections were reported for a total of 10 (18%) patients, including 3 cases of shingles, 1 metapneumovirus pneumonia, 1 urinary tract infection, 1 intra-abdominal collection presumed infectious, 3 sigmoiditis in a single patient, 1 pharyngitis, and 2 unspecified infections. The infection rate was significantly higher for IFX than for ADA (21.4% vs 4.0%;  $\chi^2$ ,  $P = .0015$ ). One death, attributed to complications from coronavirus disease 2019, occurred 26 months after IFX discontinuation.

### Discussion

This narrative review evaluated 12 studies published between 2018 and 2024, including 5 retrospective studies, 2 case series, and 5 case reports, encompassing a total of 240 patients with suspected or confirmed CS. Of these 240, 100 (42%) patients were treated with ADA at a dosage of 40 mg every other week for more than half of the patients. ADA was generally initiated for refractory CS, characterized by persistent cardiac <sup>18</sup>F-FDG uptake or worsening symptoms. The majority of patients exhibited stable or improved LVEF, including those with LVEF  $\leq 35\%$ . Follow-up



**Table 3** Outcomes and adverse events of patients treated with adalimumab

Study	LVEF (%) before vs after ADA initiation, mean $\pm$ SD or (range)	Follow-up cardiac <sup>18</sup> F-FDG uptake after ADA initiation	Arrhythmia or high-grade AVB before vs after ADA initiation	PDN dosage (mg/d) reduction/discontinuation before vs after ADA initiation or subgroup comparison	Adverse events related to ADA and death
<i>Retrospective observational studies</i>					
Baker et al <sup>15</sup>	No subgroup analysis for ADA*	No subgroup analysis for ADA*	NA	No subgroup analysis for ADA*	No serious adverse event or death reported
Frischknecht et al <sup>16</sup>	51 vs 53 ( $P = .012$ ) $\leq 35\%$ : 3 vs 2	Complete resolution at first follow-up (n = 10): 8 (80%) Inactive or remitting disease: - ADA as second-line treatment (n = 15): 15 (100%) - Last follow-up (n = 31): 26 (84%) Reduction in: - CMA: from $437 \pm 344$ to $125 \pm 158$ , $P = .026$ - SUV <sub>max</sub> : from $9.3 \pm 7.7$ to $4.2 \pm 3$ , $P = 0.13$	NA	PDN dosage: $7.3 \pm 5.1$ mg/d in the ADA group vs $9.9 \pm 5.2$ mg/d in the AZA group, $P > .05$	No serious adverse event reported 1 death under ADA (stroke)
Gilotra et al <sup>17</sup>	No subgroup analysis for ADA*	No subgroup analysis for ADA*	No subgroup analysis for ADA*	No subgroup analysis for ADA*	1 Aseptic meningitis with discontinuation of ADA 1 <i>Mycobacterium avium</i> complex infection No death reported
Churchill et al <sup>18</sup>	No subgroup analysis for ADA*	No subgroup analysis for ADA*	NA	PDN dosage reduction; $-4.7 \pm 7.7$ mg/d in the ADA group vs $-1.7 \pm 12.3$ mg/d in the IFX group at a median time of 6.7 mo, $P = .052$	Infectious complications (n = 15): 1 (7%) Discontinued because of adverse events (n = 18): 3 (17%) No death reported
Rosenthal et al <sup>19</sup>	NA	Complete resolution: 12 (63%) Partial response: 4 (21%) No response: 3 (16%)	No VT or new-onset AVB under ADA	NA	1 Lung infection No death reported
<i>Case series</i>					
Sweis et al <sup>20</sup>	44.7 (23–60) vs 49.4 (30–60) $\leq 35\%$ : 3 vs 1	Complete resolution (n = 6): 4 (67%) Partial resolution (n = 6): 2 (33%)	NA	At last follow-up: Discontinued: 5 (71%) Dosage reduction: 2 (29%); 7.5 vs 1.25 and 8.75 vs 2.0 mg/d)	No serious adverse event or death reported
Stievenart et al <sup>21</sup>	50, 65 vs 50, NA $\leq 35\%$ : 0 vs 0	NA	NA	No PDN at ADA initiation	No serious adverse event or death reported
<i>Case reports</i>					
Saab et al <sup>22</sup>	32.5 vs 52.5	Complete resolution	NA	"High dosage" vs discontinuation	No serious adverse event or death reported

Theodore et al <sup>23</sup>	26 vs 45	Complete resolution	Resolution of VT	NA	No serious adverse event or death reported
Krishnan et al <sup>24</sup>	≤35 (required LVAD). Stable at last follow-up (no value)	Complete resolution	NA	NA	1 Cellulitis No death reported
Li et al <sup>25</sup>	NA	Complete resolution	Third- vs first-degree AVB Reduction of nsVT	50 vs 15 mg/d	No serious adverse event or death reported
Vasquez and Andrade-Bucknor <sup>26</sup>	40 vs 45	NA	NA	30 mg/d vs discontinuation	No serious adverse event or death reported

ADA = adalimumab; AVB = atrioventricular block; AZA = azathioprine; CMA = cardiac metabolic activity; IFX = infliximab; LVAD = left ventricular assist device; LVEF = left ventricular fraction ejection; NA = not available; nsVT = nonsustained ventricular tachycardia; PDN = prednisone; SUV<sub>max</sub> = maximum standardized uptake value; TNFi = tumor necrosis factor inhibitor; VT = ventricular tachycardia.

\*See Table 4: outcomes for patients treated with TNFi (ADA or IFX).

PET-CT imaging demonstrated a substantial reduction in <sup>18</sup>F-FDG uptake in most patients, suggesting a favorable impact on inflammation. In addition, corticosteroid dosages were substantially reduced in most cases, highlighting the potential corticosteroid-sparing effect of ADA. For safety, we reported a significantly lower infection rate with ADA than with IFX (4% vs 21.4%;  $P = .0015$ ). While these findings suggest that ADA may offer a safer profile regarding infections, we acknowledge the limitations of the available data. The absence of prospective studies and the scarcity of data addressing patients with sarcoidosis prevent us from drawing definitive conclusions or generalizing this observation.

### Genetic insights and mechanisms of action of TNF inhibitors in sarcoidosis

TNF is a key pro-inflammatory cytokine produced by immune and nonimmune cells, including macrophages, lymphocytes (eg, T cells and natural killer cells), and fibroblasts, which plays a pivotal role in the formation and maintenance of granulomas, the hallmark of sarcoidosis.<sup>2-4</sup> Miedema et al<sup>5</sup> demonstrated that circulating naive CD4+ T cells from patients with sarcoidosis exhibited an activated phenotype, with increased CD25 expression and TNF production, compared with healthy controls, both spontaneously and under stimulation.

TNF inhibitors such as ADA and IFX disrupt this inflammatory signaling by binding to TNF, thereby preventing its interaction with receptors and reducing granulomatous inflammation. In sarcoidosis, these agents often lead to improved imaging outcomes and decreased reliance on corticosteroids.<sup>8,28</sup>

From a genetic perspective, the *TNFA2* allele has been associated with CS in Japanese individuals.<sup>29</sup> Furthermore, the TNF- $\alpha$ -308A/G polymorphism has been linked to sarcoidosis susceptibility<sup>6</sup> and response to TNF inhibitors, with a 3-fold greater response observed for patients without the variant allele (GG genotype).<sup>30</sup> However, this association has only been described in European populations, lacks validation in African-American or Asian populations, and has not been assessed specifically in CS. As such, current evidence does not support genetic testing as a reliable tool to guide therapy for CS. Precision medicine strategies, including genetic testing, remain investigational until more robust and validated data become available. Methotrexate continues to be the recommended first-line corticosteroid-sparing agent while ongoing research seeks to fill these knowledge gaps.

### Efficacy of TNF inhibitors in sarcoidosis

Of the TNF inhibitors, ADA and IFX have demonstrated the greatest efficacy for the treatment of refractory sarcoidosis.<sup>8,28</sup> While their biosimilars have primarily been studied in rheumatic and inflammatory bowel diseases,<sup>31</sup> emerging evidence suggest benefits in refractory sarcoidosis as well.<sup>32,33</sup> Conversely, etanercept, a fusion protein that inhibits TNF by binding to its receptor, performed poorly in

a nonrandomized trial of pulmonary sarcoidosis, resulting in the study's termination.<sup>34</sup> Moreover, etanercept has been associated with a greater rate of drug-induced sarcoidosis-like reactions as compared with ADA or IFX.<sup>35</sup> Golimumab, a fully human anti-TNF monoclonal antibody, indicated no significant efficacy in pulmonary or cutaneous sarcoidosis in a randomized controlled trial,<sup>36</sup> and certolizumab pegol, a polyethylene glycol-ylated fragment of a humanized anti-TNF antibody, has not been studied in sarcoidosis. Consequently, ADA and IFX remain the preferred TNF inhibitors for managing refractory sarcoidosis.

### Current guidelines and insurance challenges

Recent clinical and scientific statements by the ESC<sup>9</sup> and the American Heart Association<sup>10</sup> outline stepwise approaches to CS management, emphasizing corticosteroids as the cornerstone of treatment. Nonbiologic DMARDs, particularly methotrexate, are recommended during the initial phase because of their abilities to mitigate high relapse rates associated with corticosteroid tapering and reduce the adverse events of prolonged corticosteroid use. TNF inhibitors such as IFX and ADA are typically reserved for refractory cases or when nonbiologic DMARDs are contraindicated or not tolerated. However, growing evidence suggests that TNF inhibitors could serve as first-line corticosteroid-sparing agents in select cases in which nonbiologic DMARDs prove insufficient or ineffective. Limitations such as the absence of predictive biomarkers, the inability to stratify patients likely to benefit, and insurance constraints complicate their broader application, highlighting the need for further research to refine treatment strategies and clarify the role of TNF inhibitors in CS.

A substantial barrier to the use of TNF inhibitors in sarcoidosis is the lack of regulatory approvals by the US Food and Drug Administration and the European Medicines Agency, which may restrict reimbursement by third-party payers and delay access. This regulatory gap, compounded by high costs and stringent insurance requirements, often necessitates proof of failure with nonbiologic DMARDs, also delaying treatment initiation. While biosimilars have reduced costs in some settings, their impact on patient affordability and access remains inconsistent. ADA's subcutaneous administration offers convenience and potential cost savings compared with IFX's infusions, but these benefits are undermined by variability in co-payments and the absence of robust cost-effectiveness studies specific to sarcoidosis. Evidence from other conditions indicates that ADA may be more cost-effective in certain regions, such as Spain,<sup>37</sup> the United Kingdom,<sup>38</sup> and China,<sup>39</sup> but findings from the United States have revealed mixed results.<sup>40,41</sup>

### Risks and challenges associated with TNF inhibitors

Although ADA and IFX have demonstrated efficacy in controlling sarcoidosis-related inflammation, their use presents several challenges. The increased likelihood of serious infections, including tuberculosis and fungal infections, necessitates thorough pretreatment screening and careful

monitoring.<sup>42</sup> Noninfectious but potentially serious adverse events, such as aseptic meningitis and lupus-like syndromes, may also occur and can lead to discontinuation of therapy.

The potential for heart failure, especially in patients with ischemic heart disease, is a significant concern in CS. TNF plays dual roles in the heart through its receptors, TNF receptor 1 and TNF receptor 2, with distinct pathogenic and protective effects.<sup>43</sup> In nonischemic immune disorders, TNF inhibitors have been shown to reduce cardiovascular events by inhibiting systemic inflammation via TNF receptor 1, thereby mitigating atherosclerosis. However, this protective effect does not extend to patients with ischemic heart failure, where TNF inhibitors may exacerbate the condition.<sup>43</sup> The cardioprotective effects linked to TNF receptor 2 remain poorly understood but underscore the complexity of TNF signaling.

A pharmacovigilance study in Crohn's disease highlighted these risks, identifying a lower rate of heart failure associated with ADA than with IFX (heart failure-to-adverse event ratio 0.009 for IFX and 0.003 for ADA), though the overall incidence was low for both.<sup>44</sup>

These findings call for caution when using TNF inhibitors in patients with CS, particularly those with coexisting ischemic heart disease. In such high-risk cases, alternative therapies should be carefully considered, and if TNF inhibitors are introduced, close monitoring is essential. Moreover, the subcutaneous administration route may be preferable over intravenous to minimize risks such as fluid overload in patients with CS who have heart failure.

Medication adherence remains a critical but complex aspect of patient care, influenced by factors such as disease severity, comorbidities, socioeconomic status, patient education, and health care infrastructure, including insurance coverage and access to care.

### Immunogenicity and allergic reactions

ADA, a fully human IgG<sub>1</sub> monoclonal anti-TNF antibody, differs from IFX, which is a chimeric IgG1 antibody (Figure 1), in its theoretical potential for reduced immunogenicity. This distinction is supported by a meta-analysis reporting a cumulative incidence of antidrug antibody formation in 25.3% (95% CI 19.5%–32.3%) of patients treated with IFX compared with 14.1% (95% CI 8.6%–22.3%) of those receiving ADA.<sup>45</sup> Concomitant use of immunosuppressive agents, such as methotrexate, 6-mercaptopurine, or azathioprine, reduced the odds of developing antidrug antibodies by 74% in this meta-analysis. However, newer studies present a more complex picture. A systematic review<sup>46</sup> and an observational study<sup>47</sup> noted higher prevalences of anti-ADA antibodies at 24.9% (range 0%–87%) and 34%, respectively. These findings were based on inflammatory joint and bowel diseases, with no specific data available for sarcoidosis. The clinical impact of antidrug antibodies is significant. A systematic review of rheumatologic diseases revealed reduced clinical response rates to both ADA and IFX in patients who developed these antibodies, with patients receiving IFX also experiencing higher rates of infusion-related reactions.<sup>48</sup>

**Table 4** Outcomes of patients treated with TNF inhibitors

Study	Baseline LVEF (%), mean (range or $\pm$ SD)	Last follow-up LVEF (%) or before vs after TNFi initiation, mean (range or $\pm$ SD)	Follow-up cardiac $^{18}$ F-FDG uptake after TNFi initiation	Arrhythmia or high- grade AVB before vs after TNFi initiation	PDN dosage (mg/d) reduction/ discontinuation before vs after TNFi initiation or subgroup comparison
<i>Retrospective observational studies</i>					
Baker et al <sup>15*</sup>	48 ( $\pm$ 16) $\leq$ 35% before TNFi: 7 (based on Figure 5)	44 vs 47 (no <i>P</i> -value reported) $\leq$ 35% on TNFi: 6 (based on Figure 5)	Complete resolution at 12 mo (n=17): 17 (100%)	NA	PDN dosage (n=13): 23 vs 4 mg/d at 6 mo (no <i>P</i> -value reported)
Frischknecht et al <sup>16†</sup>	48.8 ( $\pm$ 13.3) $\leq$ 35% before TNFi: 3 (based on Figure 4)	51 vs 53 ( <i>P</i> = .012) $\leq$ 35%: 2 (based on Figure 4)	Complete resolution at first follow-up (n = 10): 8 (80%) Inactive or remitting disease: - ADA as second-line treatment (n = 15): 15 (100%) - Last follow-up (n = 31): 26 (84%) Reduction in: - CMA: from 437 ( $\pm$ 344) to 125 ( $\pm$ 158), <i>P</i> = .026 - SUV <sub>max</sub> : from 9.3 ( $\pm$ 7.7) to 4.2 ( $\pm$ 3), <i>P</i> = .13	NA	PDN dosage: 7.3 $\pm$ 5.1 mg/d in the ADA group vs 9.9 $\pm$ 5.2 mg/d in the AZA group, <i>P</i> > .05
Gilotra et al <sup>17*</sup>	48.5 ( $\pm$ 15) $\leq$ 35% before TNFi: 10 (based on Figure 2)	45 ( $\pm$ 16.5) vs 47 ( $\pm$ 15.0), <i>P</i> = .10 (n = 29) $\leq$ 35% on TNFi: 8 (based on Figure 2) LVEF decreased from 35% to 20% in 1 patient on TNFi (had progressive HF before its initiation)	Decrease in the number of segments involved: from 3.5 ( $\pm$ 3.8) to 1.0 ( $\pm$ 2.5), <i>P</i> = .008 Decrease in SUV <sub>max</sub> : from 3.59 ( $\pm$ 3.70) to 0.57 ( $\pm$ 1.60), <i>P</i> = .0005 Complete or partial resolution of $^{18}$ F-FDG uptake: 22 (73%)	VA: 13 vs 3 patients Third-degree AVB: 5 vs 5 patients	PDN dosage: 21.7 $\pm$ 17.5 mg/d vs 10.4 $\pm$ 6.1 mg/d at 6 mo (n = 33), <i>P</i> = .001 and vs 7.3 $\pm$ 7.3 mg/d at 12 mo (n = 17), <i>P</i> = .002
Churchill et al <sup>18*</sup>	54 ( $\pm$ 10) $\leq$ 35%: NA	52 (n=24) vs 51.5 (n=19) at a median time of 14 mo, <i>P</i> > .05 52 (n=24) vs 54 (n=11) at a median time of 20.5 mo, <i>P</i> > .05 $\leq$ 35%: NA	Decrease in the number of segments involved (n = 31): from 4.8 to 3.1 at a median time of 6.7 (IQR 6–8) mo, <i>P</i> = .026	NA	PDN dosage: 18.6 $\pm$ 15.7 mg/d vs 7.7 $\pm$ 12.4 mg/d at a median time of 14 mo, <i>P</i> = .018
Rosenthal et al <sup>19†</sup>	53.4 ( $\pm$ 12.3) $\leq$ 35%: NA	NA $\leq$ 35%: NA	Complete resolution: 12 (63%) Partial response: 4 (21%) No response: 3 (16%)	No VT or new-onset AVB while treated with ADA	NA
<i>Case series<sup>†</sup></i>					
Sweis et al <sup>20</sup>	44.7 (23–60) $\leq$ 35% before ADA: 3	49.4 (30–60) $\leq$ 35% on ADA: 1	Complete resolution (n = 6): 4 (67%) Partial resolution (n = 6): 2 (33%)	NA	At last follow-up: Discontinued: 5 (71%) Dosage reduction: 2 (29%; 7.5 vs 1.25 and 8.75 vs 2.0 mg/d)

(Continued)

**Table 4** (Continued)

Study	Baseline LVEF (%), mean (range or $\pm$ SD)	Last follow-up LVEF (%) or before vs after TNFi initiation, mean (range or $\pm$ SD)	Follow-up cardiac <sup>18</sup> F-FDG uptake after TNFi initiation	Arrhythmia or high-grade AVB before vs after TNFi initiation	PDN dosage (mg/d) reduction/discontinuation before vs after TNFi initiation or subgroup comparison
Stievenart et al <sup>21</sup>	50, 65 ≤35% before ADA: 0	50, NA ≤35% on ADA: 0	NA	NA	No PDN at ADA initiation
<i>Case reports</i> <sup>†</sup>					
Saab et al <sup>22</sup>	32.5	52.5	Complete resolution	NA	"High dosage" vs discontinuation
Theodore et al <sup>23</sup>	26	45	Complete resolution	Resolution of VT	NA
Krishnan et al <sup>24</sup>	≤35 (required LVAD)	Stable (no value)	Complete resolution	NA	NA
Li et al <sup>25</sup>	NA	NA	Complete resolution	Third- vs first-degree AVB	50 vs 15
Vasquez and Andrade-Bucknor <sup>26</sup>	40	45	NA	Reduction of nsVT	30 vs discontinuation

ADA = adalimumab; AVB = atrioventricular block; AZA = azathioprine; CMA = cardiac metabolic activity; <sup>18</sup>F-FDG = <sup>18</sup>F-fluorodeoxyglucose; HF = heart failure; IQR = interquartile range; LVAD = left ventricular assist device; LVEF = left ventricular fraction ejection; NA = not available; nsVT = nonsustained ventricular tachycardia; PDN = prednisone; SUV<sub>max</sub> = maximum standardized uptake value; TNFi = tumor necrosis factor inhibitor; VA = ventricular arrhythmia; VT = ventricular tachycardia.

\*Studies with efficacy outcomes, including both ADA and infliximab (no subgroup analysis performed).

<sup>†</sup>Studies with efficacy outcomes, specifically focused on patients treated with ADA.

These findings suggest that while ADA may have a lower immunogenic potential than IFX, the formation of antidrug antibodies remains a clinically relevant concern, particularly in sarcoidosis, where specific data are currently lacking. Further studies are warranted to understand the immunogenic profiles of these therapies in sarcoidosis and their impact on treatment outcomes.

A retrospective study of 142 patients with sarcoidosis treated with IFX reported antibody formation or severe adverse events, including allergic reactions, in 19 (13%) patients, prompting their transition to ADA.<sup>49</sup> During follow-up periods of 6 and 12 months after switching to ADA, none of these patients reported allergic reactions. Similarly, Sandborn et al<sup>50</sup> studied 24 patients with Crohn's disease who lost responsiveness to or developed hypersensitivity reactions to IFX; and all patients tolerated ADA without acute or delayed hypersensitivity reactions. Finally, a retrospective analysis of 671 patients with autoimmune or autoinflammatory diseases reported significantly lower rates and severity of hypersensitivity reactions with ADA (3.5%) than with IFX (13.8%).<sup>51</sup>

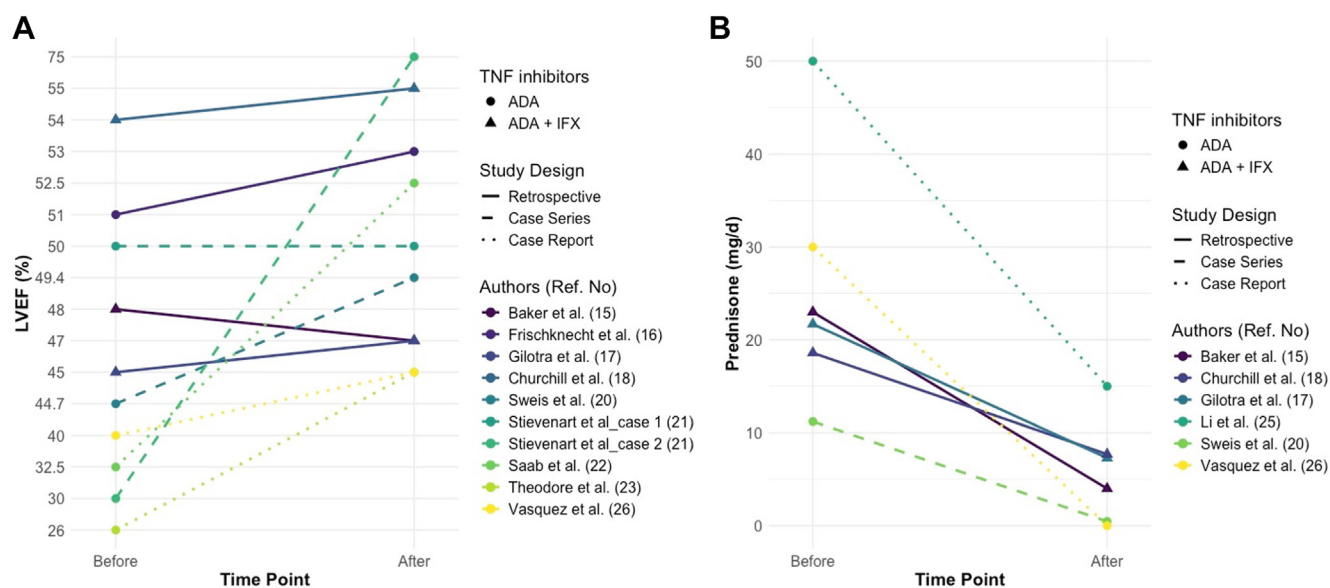
### Efficacy of adalimumab in patients with overweight

ADA differs from IFX in its administration method, with ADA delivered as a fixed subcutaneous dose (40 or 80 mg) at intervals determined by clinical response (every other week or weekly), whereas IFX is administered intravenously on the basis of patient weight. This distinction raises concerns regarding the efficacy of ADA in overweight or obese patients, whose clinical responses may be influenced by body mass index. A retrospective study of 130 patients with Crohn's disease found that body mass index  $\geq 30$  kg/m<sup>2</sup> was significantly associated with loss of response to ADA and an increased need for dosage adjustments. This trend was not observed with IFX, which uses weight-based dosing.<sup>52</sup> Similarly, a cross-sectional study of 57 patients with axial ankylosing spondylitis revealed that obesity was linked to reduced ADA drug concentrations and diminished clinical efficacy, although no increase in immunogenicity was detected.<sup>53</sup> Further supporting these findings, a meta-analysis comprising 19,372 patients (23% obese) treated with TNF inhibitors for rheumatic diseases demonstrated that obesity increased the likelihood of therapy failure by 60% (odds ratio 1.60; 95% CI 1.39–1.83; I<sup>2</sup> = 71%).<sup>54</sup>

### Infliximab in cardiac sarcoidosis

A recent systematic review of 7 retrospective studies involving 152 patients with CS who had a mean follow-up period ranging from 12 to 54.75 months concluded that IFX is a relatively safe third-line therapy.<sup>55</sup> Indeed, it was associated with a significant improvement in cardiac <sup>18</sup>F-FDG uptake, a reduction in prednisone dosage, and stability or improvement in LVEF. In addition, enhancements were observed in conduction abnormalities and ventricular tachycardia burden. Despite these benefits, adverse events were reported in 20.3% of patients (28 of 138), with severe





**Figure 3** LVEF (panel A) and prednisone dosage (panel B) before vs after TNF-inhibitor initiation. **A:** For retrospective studies, LVEF is expressed as a mean. The  $P$  value was  $<.05$  for Frischknecht et al.<sup>16</sup> The time between the 2 values varies from 6 months to  $>2$  years, depending on the follow-up period of each study (refer to Table 4 for details). **B:** For retrospective studies, prednisone dosage is expressed as a mean. The  $P$ -value was  $<.05$  for Gilotra et al.<sup>17</sup> and Churchill et al.<sup>18</sup> The time between the 2 values also varies from 6 months to  $>2$  years, depending on the follow-up period of each study (refer to Table 4 for details). ADA = adalimumab; IFX = infliximab; LVEF = left ventricular ejection fraction; TNF = tumor necrosis factor.

infections accounting for 53.6% of these events (15 cases). This underscores the need for careful patient monitoring during IFX therapy to mitigate potential risks. However, the findings of this systematic review share similar limitations with ours, including substantial heterogeneity and lack of standardized outcome measures.

In summary, both ADA and IFX lack high-quality evidence in CS and no head-to-head comparisons exist to define their relative efficacies. While ADA holds promise as a viable alternative to IFX, current evidence is limited to retrospective studies and case reports, suggesting that ADA can reduce cardiac  $^{18}\text{F}$ -FDG uptake, safely decrease corticosteroid dosages, and stabilize or improve LVEF, all with a lower reported infection rate than IFX. However, challenges such as potential risks in those with ischemic heart disease and the variability in response due to immunogenicity and body weight remain unresolved. The limitations of available data, including high heterogeneity, variability in diagnostic criteria, and absence of standardized outcomes make it difficult to draw definitive conclusions. Nevertheless, as with many rare diseases where prospective studies are challenging to conduct, these data still provide valuable insights to guide clinical decision making and inform future research. Addressing gaps through multicenter prospective trials is essential to better define ADA's role, optimize dosing strategies, and evaluate long-term safety and efficacy.

## Limitations

We acknowledge several limitations in this review that hinder drawing definitive and generalizable conclusions, highlighting the inherent challenges of studying a rare and

heterogeneous condition such as CS. The reliance on retrospective studies, case series, and case reports introduces publication bias. The aggregation of ADA and IFX data in 3 studies obscures ADA-specific outcomes, emphasizing the importance of separate analyses. Variations in dosing regimens and follow-up durations further hinder insights into the long-term efficacy and safety of ADA. In addition, variability in diagnostic criteria, treatment protocols, follow-up durations, and the absence of standardized outcome measures complicate meaningful comparisons and limits the robustness of the findings. Including patients with suspected isolated CS, while adding heterogeneity, mirrors real-world clinical practice where biopsy confirmation is often unfeasible. Excluding such cases would disregard a key patient subgroup requiring investigation.

Confounding factors, such as the use of antiarrhythmic drugs, heart failure therapies, and the interplay of inflammation and fibrosis, are inconsistently addressed, complicating assessments of TNF inhibitors' effects on arrhythmias.

PET outcomes present another limitation, with variability in standardized uptake value measurements and a lack of consensus on clinically meaningful changes complicating interpretation of the results. Inconsistent dietary preparation protocols between studies exacerbate this issue, potentially leading to false-positive findings. Standardized imaging protocols are urgently needed to improve the reliability and comparability of PET results.

Variability in imaging modalities (eg, echocardiography, cardiac magnetic resonance imaging, and nuclear imaging) likely influenced the reported LVEF values, as each modality has inherent differences in accuracy and reproducibility. In addition, the threshold for clinically meaningful changes in



LVEF, such as a 5% or 10% improvement, was not explicitly defined or standardized across studies.

The definition of refractory CS varies significantly across studies, often relying on subjective criteria such as persistent or worsening PET activity or cardiac symptoms. This variability, combined with the challenge of distinguishing inflammation from fibrosis as drivers of disease progression, complicates the interpretation of treatment responses and outcomes. A validated, universally accepted definition of refractory CS is essential for consistent research and clinical practice.

These limitations underscore the inherent difficulties of studying CS and highlight the urgent need for multicenter collaboration and prospective trials with standardized protocols to clarify ADA's role in managing this complex disease.

## Conclusion

CS remains a challenging condition with substantial risks of heart failure, arrhythmias, and sudden death, requiring effective and well-tolerated treatments. Both ADA and IFX have shown promise in managing refractory CS, but limitations of the available data apply to both agents. ADA emerges as a valuable option, potentially offering a safer profile, particularly with respect to infection-related complications.

While the evidence is restricted to retrospective studies, as is often the case in rare diseases, it provides valuable insights to inform clinical practice and guide future research. However, gaps remain in the optimal timing, choice, dosage, and duration of TNF inhibitors. These challenges are further complicated by factors such as obesity, immunogenicity, ischemic heart failure, as well as disparities in care access and insurance coverage. Addressing these gaps will require robust, multicenter collaboration to conduct prospective trials and establish standardized protocols, ultimately improving outcomes for patients with this complex and rare condition.

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## Appendix Supplementary Data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hroo.2024.12.012>.

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