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# Controversies in the Treatment of Cardiac Sarcoidosis

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**Abstract.** There are many challenging aspects of the management of cardiac sarcoidosis (CS) with corticosteroids and other immunosuppressive therapy (IST). First, it is not always clear who will benefit from therapy or when to initiate treatment. Secondly, there are no randomized controlled trials or large prospective studies to guide what medications to use, at what doses, and for how long. The European Respiratory Society (ERS) clinical practice guidelines on the treatment of sarcoidosis makes a strong recommendation for the use of immunosuppressive therapy in CS patients with functional cardiac abnormalities, including heart blocks, dysrhythmias, or cardiomyopathy where patients are considered at-risk of adverse outcomes. Corticosteroids are the first line immunosuppressive therapy in CS however, early initiation of second-line steroid sparing medications has been advocated and there is data to suggest that concomitant initiation of therapy may be more beneficial. The use of anti-tumor necrosis factor (anti-TNF) agents (including infliximab and adalimumab) considered beneficial third-line anti-sarcoidosis treatment agents in other severe refractory manifestations of disease remains controversial.

**Key words:** cardiac sarcoidosis, corticosteroids, immunosuppressive therapy, anti-TNF agents in cardiac sarcoidosis

## Introduction

There are many challenging aspects of the management of cardiac sarcoidosis (CS) with corticosteroids and other immunosuppressive therapy (IST). First, it is not always clear who will benefit from therapy, when to initiate treatment and for how long to treat. Secondly, there are no randomized controlled trials or large prospective studies to guide what medications to use, at what doses, for how long.

As with other organ manifestations, the concept behind the use of corticosteroids and other IST in CS is to control/reverse ongoing active inflammation, prevent disease progression and avoid complications(1). The European Respiratory Society (ERS) clinical practice guidelines on the treatment of sarcoidosis(2) makes a strong recommendation for the use of immunosuppressive therapy in CS patients with functional cardiac abnormalities, including heart blocks, dysrhythmias, or cardiomyopathy where patients are considered at-risk of adverse outcomes(2).

Corticosteroids are the first line immunosuppressive therapy in CS however, early initiation of second-line steroid sparing medications has been advocated and there is data to suggest that concomitant initiation of therapy may be more beneficial(1-5). The most prescribed second-line steroid-sparing agents in CS include methotrexate, azathioprine, mycophenolate mofetil, leflunomide and cyclophosphamide(2, 3, 6-9). The use of anti-tumor necrosis factor (anti-TNF) agents (including infliximab and adalimumab) considered beneficial third-line anti-sarcoidosis treatment agents in other severe

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refractory manifestations of disease remains controversial(2, 10-12).

This review will address some of the controversies in the treatment of CS. Specifically, we will address the following:

i. Which patient with CS should be treated with immunosuppressive therapy?
ii. What immunosuppressive therapy should be used in patients with CS and what is the evidence behind use of these immunosuppressive therapies?
iii. When should corticosteroids and other immunosuppressive therapy be initiated?
iv. What is the optimal initial prednisone dose in CS?
v. Use of prednisone PLUS methotrexate (or other cytotoxic) as initial therapy in CS?
vi. What is the role of pulse dose methylprednisolone in CS?
vii. What is the role of Infliximab and other anti-TNF therapy in CS?
viii. What other Immunomodulators have been used in CS?
ix. Algorithmic Approach to treatment of CS.
x. Duration of therapy in CS?
xi. Conclusion

It is hoped that addressing these controversial topics will provide some guidance to clinicians caring for CS patients and build a framework upon which future studies in CS can be predicated.

*I. Which patient with CS should be treated with immunosuppressive therapy?*

The recently published European Respiratory Society (ERS) clinical practice guidelines on the treatment of sarcoidosis makes a strong recommendation for the use of immunosuppressive therapy in CS patients with "*clinically relevant cardiac disease*"(2). Although no clear-cut definition of "clinically relevant cardiac sarcoidosis" exists, the guidelines describe this as CS patients with "**functional cardiac abnormalities**, including heart blocks, dysrhythmias, or cardiomyopathy **where patients are considered at-risk of adverse outcomes**"(2). While the recommendation for this strategy was strong, the quality of supporting evidence was very low(2, 13). The reason for this strong recommendation despite the very low quality of supporting evidence is the high morbidity and mortality associated with CS(2, 14-17). The supporting evidence were case series and retrospective studies.

Table 1 adapted from the ERS guidelines(2) lists the features in CS patients that have been associated with increased mortality and worse outcomes and Table 2 summarize the indications for immunosuppressive therapy in CS patients(2, 6, 7). The most well-established independent mortality predictors in CS include complete heart block (CHB)(18-22), sustained ventricular tachycardia (VT)(2, 9, 23), and congestive heart failure (CHF)(23-25). While features, such as a positive $^{18}$F-FDG PET scan(26-28) and extensive late gadolinium enhancement (LGE) (21, 29, 30) have been linked in some studies to increased morbidity and mortality, they are still under investigation and may also be independent markers for increased mortality(2).

Complete or advanced (high-grade) atrioventricular blocks (AVB) are the most common conduction abnormalities in CS patients and are associated with poor outcomes(7, 18-22, 31, 34-37). Nordenswan(20) and Takaya(18) and colleagues showed that the risk of fatal and non-fatal adverse cardiac events (including sudden cardiac death) was significantly elevated in CS patients presenting with high-grade AVB with or without concomitant ventricular tachycardia or LV dysfunction(18, 20). Using data from the Myocardial Inflammatory Disease Registry in Finland, Nordenswan and colleagues(20) found that of 325 cases of CS diagnosed in Finland between 1988 and 2015, 143 patients (44%) presented with complete or high-grade AVB and 24% of patients who presented with isolated AVB (without concomitant VT or left ventricular (LV) dysfunction) experienced a fatal or aborted sudden cardiac death(20). The 5-year incidence of sudden cardiac death in that study was 9% for patients with isolated AVB and 14% to 34% if they had associated non-severe (35% - 50%) or severe LV dysfunction (left ventricular ejection fraction (LVEF) $<$ 35%). Similarly, Takaya and colleagues(18) found that over a median follow-up period of 34-months, CS patients who presented with isolated complete or high-grade AVB had a high rate of major fatal and non-fatal adverse cardiac events defined as cardiac death, ventricular fibrillation, sustained VT and hospitalization for heart failure(18). Twelve of 22 CS patients (55%) who presented with isolated complete

**Table 1.** Poor Prognostic Indicators in Patients with Cardiac Sarcoidosis(2)

| Variable | Prognostic association | References |
|---|---|---|
| Age at diagnosis > 50 years | Increased mortality risk | (9, 21) |
| LVEF < 40%<br>Increased LV end-diastolic diameter<br>Abnormal longitudinal strain on Echocardiography<br>Interventricular septal thinning | Increased mortality risk | (8, 9, 21, 23, 31)<br>(23)<br>(32) |
| Complete heart block and high grade AVB | Increased mortality and as a mechanism of sudden deaths.<br>Increased risk of relapse and less favorable course of CS. | (18-22)<br>(24) |
| Sustained ventricular tachycardia | Increased mortality risk | (23) |
| Late Gadolinium Enhancement (LGE) on cMRI | Increased risk of cardiovascular death & ventricular arrythmia.<br>Extensive LGE has been associated with lack of improvement in LV function after steroid therapy. | (21, 29, 30) |
| Cardiac inflammation and abnormal perfusion defect identified by positive 18F FDG-PET | Increased risk of ventricular tachycardia & mortality. | (26-28) |
| Elevated troponin or brain natriuretic peptide (BNP) | Reduced event free survival and increased risk of adverse outcomes. | (33) |
| NYHA Functional class 3 or 4 | Increased mortality risk | (23) |

Abbreviations: LVEF = Left ventricular Ejection Fraction, NYHA = New York Heart Association, cMRI = cardiac magnetic resonance imaging, 18F FDG-PET - [(18)F] fluorodeoxyglucose (FDG) – Positron Emission Tomography scan, BNP = Brain natriuretic peptide. AVB = Atrioventricular block, CS = cardiac sarcoidosis.

**Table 2.** Indications for Immunosuppressive Therapy in CS Patients(2, 6, 7)

| | | |
|---|---|---|
| ERS guideline indications | Functional cardiac abnormalities | Heart blocks and conduction abnormalities<br>Complete Heart Block<br>High-grade AVB<br>Arrythmias<br>Sustained VT<br>Cardiomyopathy/LV Dysfunction<br>Moderate LV dysfunction (LVEF 35% to 50%<br>Severe LV dysfunction (LVEF < 35%) |
| Other possible Indications | Evidence of cardiac inflammation<br>Symptom burden<br>Abnormal serum biomarkers | Abnormal $^{18}$F FDG-PET scan<br>Extensive myocardial LGE<br>NYHA functional class III or IV symptoms<br>Elevated Troponin<br>Elevated BNP |

Key: AVB = atrioventricular block, VT = Ventricular tachycardia, LV = left ventricular, LVEF = left ventricular ejection fraction, cMRI = cardiac magnetic resonance imaging, 18F FDG-PET - [(18)F] fluorodeoxyglucose (FDG) – Positron Emission Tomography scan, BNP = brain natriuretic peptide

or high-degree AVB had a major adverse cardiac event and this was fatal in seven patients (41%)(18). The predictors of fatal cardiac events in patients with isolated complete or high-degree AVB were presence of New York Heart Association (NYHA) functional class III or IV symptoms and an elevated plasma B-type natriuretic peptide (BNP > 150 pg/mL)(18).

Presence of LV dysfunction and sustained VT are also independent mortality predictors in CS patients (8, 9, 18, 20, 21, 23, 31). In the studies by Zhou(9) and Yazaki(23) and colleagues, CS patients presenting with LVEF < 40% had 2.4-fold increased odds of death or cardiac transplant during a median follow-up period of 8.8 years(9), and presence of sustained VT was associated with a 7.2-fold increased hazard of death during a mean follow-up of 5.7 years(23). One study also found that the 10-year survival rate of CS patients with LVEF > 50% was

89% vs. 27% for those with LVEF < 50%. In that study, CS patients diagnosed at autopsy were more likely to have significantly reduced LVEF, severe heart failure symptoms, a higher incidence of CHB and sustained VT(23).

It is to be noted that by recommending treatment for the most well-established morbidity and mortality predictors in CS, the ERS guidelines have linked treatment decisions in CS patients to outcomes(2).

*II. What immunosuppressive therapy should be used in patients with CS?*

## Corticosteroids

Corticosteroids are the first line immunosuppressive therapy in CS(1-3). The best data in support of corticosteroid use in CS relates to AV conduction abnormality, and recovery of left ventricular function (4, 6, 24, 38-41). Corticosteroids have also been used in CS patients with ventricular arrythmias, however data in support of this practice is less robust.

A systematic review conducted by Sadek and colleagues(39) evaluated 73 patients with CS and AV conduction abnormality and found that 27 of the 57 patients (47.4%) treated with corticosteroids improved; while no improvement was noted in all of the 16 patients not treated with corticosteroids(39). A more recent review by the same group found that of 178 CS patients with high-grade AVB treated with corticosteroids and other IST, 76 (42.6%) had AV nodal conduction recovery while none of the 21 patients not treated with immunosuppressives had AV nodal recovery(38). Patients with high degree AVB (Mobitz II) were more likely to respond to therapy in comparison to patients with complete AVB(42). Late initiation of therapy, presence of impaired LV function, and presence of interventricular septal thinning were associated with poor response to therapy(18, 43). Table 3 lists some of the factors associated with a potential improvement of CS in response to corticosteroid therapy in CS patients presenting with AV nodal disease(18, 43).

Several studies have reported on the effect of corticosteroids and/or IST in CS patients presenting with LV dysfunction. Chiu and colleagues(44) found that in patients with initial LVEF ≥55%, long-term steroid therapy prevented decline in LV function and LV remodeling. Patients with LVEF <55% showed significant LVEF improvement, however, in patients with LVEF <30%, steroid therapy resulted in neither LV volume reductions nor improvement(44). Other studies have however, observed significant improvement in LVEF with corticosteroid therapy in patients with severe LV dysfunction(9, 31, 45). Zhou and colleagues evaluated 27 patients with CS and severe LV dysfunction and found that patients with pretreatment LVEF < 40% improved with corticosteroid therapy given in combination with medical management for congestive heart failure(9). A recent systematic review that evaluated 12 studies (n=324 patients)(38) in which CS patients received corticosteroids or other IST for mild to moderate LV systolic dysfunction (LVEF 31% to 50%), found that there was an improvement in mean LVEF in 5 out of 12 studies (n=117)(29, 44, 46-48), no change in 6 out of 12 studies (n=177)(12, 31, 45, 49-51), and a mean decline in one study (n=20)(52). Some of the factors influencing response to IST in CS patients with LV dysfunction include degree of LV dysfunction, presence of active myocardial inflammation(44), minimal myocardial scarring(29), extent of LGE on cMRI(4, 38), and early vs. late initiation of corticosteroid therapy(48). Table 4 summarizes the factors associated with favorable response to corticosteroid and other immunosuppressive therapy in CS patients presenting with LV dysfunction. Nagai and colleagues(48) found that early initiation of corticosteroid therapy improved clinical outcomes even in patients without evidence of active myocardial inflammation(48).

There are conflicting results on the efficacy of corticosteroids in CS patients with ventricular

**Table 3.** Factors associated with potential improvement in response to immunosuppressive therapy in CS patients presenting with AV Conduction Abnormalities(18, 43)

1. Initiation of therapy within first six months
2. Presence of Mobitz II block (vs. CHB)
3. Normal or minimally impaired LV function
4. Evidence of myocardial inflammation
   a. Abnormal $^{18}$F-FDG PET uptake
   b. Increased T-2 weighted signal in addition to LGE on cMRI

Abbreviations: CHB = complete heart block, cMRI = cardiac magnetic resonance imaging, LV = Left ventricular, $^{18}$F FDG-PET - [(18)F] fluorodeoxyglucose (FDG) – Positron Emission Tomography scan, CS = cardiac sarcoidosis, LGE = late gadolinium enhancement.

arrythmias. While some studies showed a benefit of immunosuppressive therapy in CS patients who present with ventricular arrythmias (46, 53-57), others did not(41, 52, 58, 59). Fazelpour and colleagues(38) evaluated data from 8 studies that included 129 CS patients who received corticosteroids for ventricular arrythmias. Five of the studies(46, 55, 56, 60, 61) reported on sustained VT while three(41, 52, 53) reported on the burden of premature ventricular contractions (PVCs) and nonsustained VT (NSVT). Of the 69 patients who received corticosteroids (or other immunosuppressive therapy) for sustained VT, 32 (46%) had recurrent sustained VT similar to 3/7 (43%) of patients who did not receive corticosteroids (38). Similarly, there was no change in the PVC burden(41, 53) or prevalence of NSVT(53) in two of the three studies that evaluated that outcome. Medor and colleagues(52) found a paradoxical worsening of ventricular arrythmias (increased burden of PVCs and NSVT) in CS patients treated with immunosuppressive therapy; however, patients were not on concomitant antiarrhythmic medication during the study period(52). It has been suggested that patients with sustained VT may not be responsive to IST because VT develops in the advanced stage of disease and is associated more with areas of myocardial scarring promoting reentry mechanisms than to areas of myocardial edema and active inflammation(41, 53, 62, 63). Naruse and colleagues(57) evaluated 37 CS patients with sustained VT and found that only 12/34 (35%) patients who received corticosteroids had recurrence of VT(57). Absence of gallium-67 myocardial uptake (suggestive of absent myocardial inflammation) before corticosteroid therapy was the only independent predictor for VT recurrence(57). Yalagudri and colleagues(56) also found that 13/14 (93%) CS patients who presented with VT and increased myocardial $^{18}$F-FDG-PET uptake had resolution of VT with IST given concomitantly with anti-arrhythmic drug (AAD) therapy and ICD implantation. Table 5 lists the factors that have been associated with favorable response to corticosteroids and immunosuppressive therapy in CS patients presenting with ventricular arrythmias.

It is to be noted that in addition to the paradoxical worsening of ventricular arrythmias in some CS patients treated with corticosteroids and other IST(52), the use of corticosteroids has also been associated with ventricular aneurysm formation in CS patients(6, 36).

## Second Line Steroid Sparing Immunosuppressive Agents Used in CS

Second line steroid sparing medications that have been used in patients with CS include methotrexate(4), azathioprine(4, 21, 64), leflunomide(65-67), mycophenolate mofetil(64, 68). and cyclophosphamide(21, 38, 40, 69, 70).

Recently published ERS consensus guidelines for the management of pulmonary sarcoidosis(1) specify that second line agents are indicated in patients with severe disease, inadequate response to corticosteroid therapy, expectation of prolonged/or high-dose corticosteroid therapy (steroid sparing), occurrence of corticosteroid toxicity or in those for

**Table 4.** Factors associated with clinical improvement in response to immunosuppressive therapy in CS patients presenting with LV dysfunction(29, 44-48)

| |
|---|
| 1. Degree of LV Dysfunction (mild dysfunction responds better) (38) |
| 2. Early initiation of corticosteroid therapy (within 6 months) of diagnosis)(45, 46, 48) |
| 3. Presence of active myocardial inflammation(44) |
| 4. Small extent of LGE (LGE mass < 20% of LV mass) on cMRI(29) |

Abbreviations: CS = cardiac sarcoidosis, LV = Left ventricle, LGE = late gadolinium enhancement, cMRI = cardiac magnetic resonance imaging

**Table 5.** Factors associated with clinical improvement in response to IST in CS patients with ventricular arrythmias(6, 46, 53, 56)

| |
|---|
| 1. Evidence of myocardial inflammation/disease activity*. |
| 2. Early initiation of treatment after diagnosis (within 1 month) |
| 3. Initiation of therapy in the early disease phase |
| 4. Preserved LVEF at time of diagnosis and initiation of therapy |

Abbreviations: *The Heart Rhythm Society (HRS) consensus statement recommend treatment only in patients with evidence of disease activity as assessed on $^{18}$F FDG-PET - [(18)F] fluorodeoxyglucose (FDG PET scan. LVEF = Left ventricular ejection fraction, $^{18}$F FDG-PET - [(18)F] fluorodeoxyglucose (FDG) – Positron Emission Tomography scan, CS = cardiac sarcoidosis.

whom corticosteroids cannot be weaned to prednisone (or prednisone equivalent) doses < 10 mg/day(1, 2). These guidelines have advocated a stepwise approach to treatment with sequential addition of medications after inefficacy has been established(1). CS is one of the most severe manifestations of sarcoidosis and there is a suggestion towards improved outcomes with early, or concomitant initiation of prednisone and other IST (discussed further below) (3, 64, 71, 72).

### Methotrexate

Methotrexate is the most widely studied and used second-line steroid sparing IST in CS(73-75). It is a folic acid antagonist which through a series of steps inhibits purine and pyrimidine metabolism, as well as amino acid and polyamine synthesis(76). Its exact mechanism of action in sarcoidosis is unclear and is thought to be predominantly anti-inflammatory mediated via adenosine (A) and $A_{2A}$ receptors on inflammatory cells(77-79). Methotrexate also inhibits several pro-inflammatory cytokines including TNF-alpha (TNF-α), interleukin- (IL-) 4, IL-13 and interferon gamma which stimulate T-cells and promote granuloma formation and expansion(76, 80). In a recent Delphi consensus study for the treatment of pulmonary sarcoidosis (1), methotrexate was recommended as the first choice non-biologic therapy in a step-wise treatment approach. Oral methotrexate was favored; however subcutaneous methotrexate was considered a reasonable alternative in patients with nausea or other gastrointestinal side-effects(1).

Data in support of the use of methotrexate in CS comes from several observational and retrospective studies. In one open-label trial directly comparing prednisone alone versus methotrexate plus initial prednisone, the addition of methotrexate was associated with long term improvement of ejection fraction and BNP after five years of therapy(72). Stievenart and colleagues evaluated 21 studies (n=950) that reported on immunosuppressive therapy in CS and found that methotrexate was the most commonly used steroid sparing second-line agent, and indications for use mirrored those for pulmonary/extra-cardiac sarcoidosis(4). The Japanese Circulation Society (JCS) guidelines on the treatment of cardiac sarcoidosis(7) make a grade C1 recommendation (recommended despite no strong supporting evidence) for the use of methotrexate as monotherapy or in combination with corticosteroids in CS patients who do not respond well to corticosteroids, cannot use them or cannot increase their dose due to adverse drug effects. The guidelines emphasize the need to monitor for adverse reactions or complications including leukopenia, hepatic or renal dysfunction and pulmonary toxicity in CS patients on methotrexate(7).

The recommended initial (as well as maintenance) dose of methotrexate in patients with sarcoidosis is 5 – 15mg/week and this should be given with folic acid at a dose of 1mg daily or 5mg weekly(74). In a large study of over 600 sarcoidosis patients treated for up to six years at one center, leukopenia and/or hepatic toxicity were seen in less than one percent of patients(81). The multinational evidence based WASOG group on the use of methotrexate in sarcoidosis advised against maintenance doses beyond 20mg per week without safety studies(74).

Methotrexate is contraindicated in pregnancy and breast feeding and should not be used by men or women for at least 3-months before a planned pregnancy(74). Patients on methotrexate should have regular monitoring of their complete blood counts (CBC), liver function tests (LFT) and renal function while on therapy(74). It is also recommended that testing for human immunodeficiency virus infection (HIV), hepatitis B/C and interferon-gamma release assay testing for Mycobacterium tuberculosis infection be performed prior to initiation of therapy(74). Other guideline recommendations for the use of methotrexate in sarcoidosis have been published(74). Table 6 provides a summary of the mechanism of action, dose and toxicities associated with methotrexate.

### Azathioprine

Azathioprine is a purine antimetabolite immunosuppressive that has been used as second line agent in CS(4, 21, 64) based on data extrapolated from its use in patients with pulmonary sarcoidosis(1, 82-84). There are no randomized or prospective studies on the use of azathioprine in CS however both the JCS(7) and the ERS(2) guidelines list azathioprine as a second-line steroid sparing agent that may be used alone or in conjunction with steroids in patients with CS (low level evidence).

**Table 6.** Corticosteroid sparing Medications in Cardiac Sarcoidosis

| Drugs | Usual Dosage | Mechanism of Action | Major Toxicity | Drug monitoring | Comments |
|---|---|---|---|---|---|
| Methotrexate | 5-15mg once a week PO Maybe given SQ if severe GI intolerance | Inhibits folate metabolism; and via A2 receptors inhibits several pro-inflammatory cytokines | GI intolerance, hepatotoxicity, leukopenia, fatigue, pneumonitis, risk of infection | Serial CBC, LFT, renal function testing Ensure negative HIV, hepatitis B/C & IGRA prior to use | Teratogenic; avoid in pregnancy & breast feeding. Folate supplementation is recommended. Cleared by kidney, avoid in significant renal failure. |
| Azathioprine | 50-200mg daily PO | Purine analog/ antimetabolite that inhibits purine synthesis necessary for B- and T-cell proliferation. | Leukopenia, hepatotoxicity, risk of infection, cutaneous and lymphoproliferative cancers. | CBC, LFT | Check TPMT level at initiation |
| Mycophenolate Mofetil | 1,000-3,000 mg daily PO | Preferentially inhibits de novo GMP synthesis in T- and B-lymphocytes thus suppressing cellular and humoral immunity | Leukopenia, risk of infection, lymphoproliferative and cutaneous cancers | CBC, LFT Negative hepatitis B/C screening 7 IGRA are required prior to initiation | Limited data supporting efficacy and use in sarcoidosis. Non-nephrotoxic |
| Leflunomide | 10-20 mg daily PO | Inhibits de novo synthesis of dUMP which is necessary for Activated T-lymphocytes to undergo clonal expansion and terminal differentiation. | Nausea, Leukopenia, Hepatotoxicity, risk of infection, skin rash, fatigue, peripheral neuropathy | CBC, LFT, renal function testing | Due to long half-life, cholestyramine may be necessary to quickly remove the drug and its metabolites in toxicity. Teratogenic, avoid in pregnancy & breastfeeding. Cleared by kidney, avoid in significant renal failure |
| Cyclophosphamide | 1 gm IV monthly | Nitrogen mustard that accelerates cell death and in lower doses decreases secretion of interferon gamma and IL-12. | Leukopenia, bone marrow suppression/ failure, risk of infections, cardiotoxicity with high doses, hepatotoxicity, pneumonitis, bladder cancer | CBC, LFT, renal function | embryo- and feto-toxic. Should be avoided in pregnant and nursing women. Also has risk of infertility. Cleared by kidney, avoid in significant renal failure |

Key: CBC = complete blood count, LFT = liver function test, HIV = human immunodeficiency virus, IGRA = interferon gamma release assay for TB, PO = per oral, SQ = subcutaneously, IV = intravenously, TPMT = thiopurine S-methyltransferase (TPMT) genotype or enzyme activity, A2 = adenosine, GMP = guanosine monophosphate - an essential nucleoside for purine synthesis during cell division, dUMP = deoxyuridine monophosphate

In 2013, Vorselaars and colleagues(85) published a retrospective study that compared the effectiveness of azathioprine versus methotrexate as second-line therapy in pulmonary sarcoidosis. They found that both drugs had similar steroid-sparing potency and similar positive effect on lung function however azathioprine was associated with a higher infection rate(85). More recent studies have also found an increased infection rate with azathioprine(86). Rossides and colleagues(86) evaluated 724 patients with sarcoidosis treated with either methotrexate or azathioprine and found that patients treated with methotrexate were 43% less likely to get an infection as compared to those who received azathioprine. The adjusted 6-month risk of infection in the methotrexate group was 6.8% compared to 12% in the azathioprine group(86).

The recommended starting/maintenance dose for azathioprine in CS patients is 50 to 200mg daily(87) (Table 6). Patients should have serial CBC and LFT checks to monitor for leukopenia and hepatoxicity(87). It is also recommended that patients undergo thiopurine S-methyltransferase (TPMT) genotype or enzyme activity testing prior to initiating therapy

because patients with reduced TPMT activity have an increased risk of developing life threatening bone marrow toxicity to azathioprine(88).

There are reports of an increased risk of cutaneous and lymphoproliferative cancers in patients treated with azathioprine(89-91) however this risk appears to be disease specific(92). There are no studies evaluating the risk of azathioprine-associated malignancy in sarcoidosis patients nonetheless, patients should be counselled about the potential increased risk of cancer prior to initiation of therapy(87).

### Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an inhibitor of inosine monophosphate dehydrogenase (IMPDH) enzyme which catalyzes the synthesis of guanosine monophosphate (GMP) - an essential nucleoside for purine synthesis during cell division - from inosine(93, 94). MMF exerts its anti-inflammatory effect in sarcoidosis and other autoimmune diseases by preferentially inhibiting IMPDH in T and B lymphocytes thereby suppressing both cellular mediated immune responses and antibody formation(93). MMF also induces apoptosis of activated T-cells and inhibits the expression of several adhesion molecules thus blocking the migration of lymphocytes and monocytes into sites of inflammation(93-95).

Evidence for the use of MMF in the treatment of CS comes from retrospective studies, case reports and case series(64, 68, 70, 96-98). Griffin and colleagues(64) retrospectively evaluated 77 patients with CS treated with prednisone monotherapy (n=32) or a combination of prednisone and MMF (n=45) and found that MMF was steroid sparing and well tolerated(64). Patients treated with MMF + prednisone had similar improvements in myocardial $^{18}$F-FDG uptake but required significantly less prednisone than patients treated with prednisone monotherapy(64). There was no difference in outcomes with respect to new sustained ventricular arrythmias, need for heart transplantation, implantation of LVAD or death(64). There was a trend towards more patients in the combination group having persistent third-degree AVB (86% vs. 25%) and requiring more ICD therapy (18% vs. 3%) however, this did not achieve statistical significance ($P = 0.09$ and 0.07 for both outcomes respectively) (64). Notably, at the end of one year, the median LVEF was higher in the combination group, than in those who received prednisone monotherapy (48% vs. 40%, $P = 0.02$)(64). Overall, MMF was well tolerated. Only 18% of patients on MMF + prednisone reported adverse effects (vs. 55% on prednisone monotherapy) and this percentage was lower than was observed with other IST in the same study(64).

MMF is non-nephrotoxic and does not induce transforming growth factor-beta (TGF-β) production which is fibrogenic(99). In the studies above, MMF was typically started at a total daily dose of 1000 – 2000 mg in combination with prednisone 30-40mg daily(64). A normal CBC, LFT, renal function and negative hepatitis B and C screening are required prior to initiating MMF(64). Patients should also undergo routine monitoring of these parameters monthly for 3 months, and if stable, may be extended to 3-monthly intervals(64) (Table 6).

### Leflunomide

Leflunomide is an immunomodulatory drug that prevents the expansion of activated and autoimmune lymphocytes by inhibiting the rate limiting mitochondrial enzyme dihydroorotate dehydrogenase (DHODH) which plays a key role in the de novo synthesis of deoxyuridine monophosphate (dUMP) (100, 101). Activated T-lymphocytes depend on pyrimidine de novo syntheses to fulfill their metabolic needs for clonal expansion and terminal differentiation into effector cells; and leflunomide inhibits this process(100, 101). There is also some evidence that leflunomide selectively suppresses IL-1 and TNF-α and downregulates the glycosylation of adhesion molecules thereby reducing cell to cell contact activation during inflammation(102).

Data on the use of leflunomide is based on several retrospective studies primarily in patients with pulmonary sarcoidosis(65-67). There are no randomized or prospective trials that have evaluated the use of leflunomide in CS patients. Leflunomide has been shown to be steroid sparing and potentially useful in sarcoidosis patients failing or intolerant to other therapies(65). Sahoo and colleagues(65) retrospectively evaluated the safety and efficacy of leflunomide in 76 patients with chronic refractory sarcoidosis including 3 (4%) patients with CS, and found that at 9 months, 2 of the 3 CS patients had complete recovery and 1 had partial recovery. This was consistent with 83% partial or good response

observed in patients with extra pulmonary sarcoidosis in general(65). Baughman and Lower also observed in an earlier study(66) that sarcoidosis patients intolerant to methotrexate (13 of 24 patients) were successfully treated with leflunomide(65).

The usual starting (and maintenance) dose of Leflunomide in sarcoidosis is 10 to 20 mg daily, however, a loading dose of 100 mg daily for three days followed by a maintenance dose of 10 to 20 mg daily has been used with minimal adverse effect(65, 66). The most common adverse events associated with leflunomide include diarrhea, nausea, bloating, hepatic enzyme elevation, neuropathy and hair loss(65). Rarely it can lead to systemic hypertension. The incidence of adverse effects was found to be much less at lower leflunomide doses (10 mg daily) used in another study(66).

There are some reports of an association between use of leflunomide and pulmonary arterial hypertension(103-105) however, a large systematic review and metanalysis including 8 randomized controlled trials (n=4579 patients) of leflunomide in patients with rheumatoid arthritis found that there was no association between leflunomide and an increased risk of infectious and non-infectious respiratory adverse events including pneumonitis and pulmonary hypertension(106).

Leflunomide is contraindicated in pregnant women and in patients with severe hepatic impairment. LFTs should be monitored monthly for at least six months after starting leflunomide and thereafter every 6 to 8-weeks (Table 6).

### Cyclophosphamide

There are several case reports of steroid refractory CS successfully treated with intravenous (IV) cyclophosphamide(21, 38, 40, 69, 70). This medication is listed as a possible second line immunosuppressive therapy for CS in the JCS guidelines(7) and acknowledged in the ERS guidelines(2) as an agent used in current clinical practice in CS patients who have continued disease or who relapse despite treatment with glucocorticoids with or without methotrexate, azathioprine, leflunomide or mycophenolate.

Cyclophosphamide is a nitrogen mustard agent that is approved by the FDA for the treatment of malignant lymphoma, multiple myeloma, breast cancer and neuroblastoma(107). It is a non-cell cycle specific anti-neoplastic and anti-mitotic agent that accelerates programmed cell death in high doses(107). At lower doses, cyclophosphamide exerts an immunomodulatory effect by a variety of mechanisms including suppressing regulatory T-cell activity, decreasing the secretion of interferon-gamma and IL-12 and increasing secretion of IL-4 and IL-10(107). Its exact mechanism of action in sarcoidosis is unclear.

Cacoub and colleagues(21) published a retrospective analysis of 157 CS patients treated with corticosteroids and other IST over a median follow up of 7-years and found that only IV cyclophosphamide was associated with a lower risk of disease relapse; however, this was compared to patients who did not receive therapy(21). In that study, patients received corticosteroids either alone (n = 79) or in association with other IST including IV cyclophosphamide (n = 79), methotrexate (n = 29), mycophenolate (n=45), hydroxychloroquine (n = 29), infliximab (n = 14) or azathioprine (n = 8)(21). 4% (n=13) of patients did not receive any therapy and constituted the comparison group(21). IV cyclophosphamide was given at a dose of 1g monthly(21).

Cyclophosphamide is embryo- and feto-toxic and should be avoided in pregnant and nursing women. It has also been associated with infertility (temporary and permanent) and patients should receive adequate education and counseling on the risks of infertility prior to initiating cyclophosphamide therapy(107). Table 6 summarizes the labs that need to be monitored in patients taking cyclophosphamide.

### *III. When should immunosuppressive therapy be initiated?*

Most studies in patients with CS showed that early initiation of immunosuppressive therapy is associated with better outcomes(22, 24, 42, 46, 53). Yodogawa and colleagues(42) observed that patients with high degree AVB (Mobitz II) had better recovery rates in comparison to patients with complete AVB suggesting that early initiation of therapy prior to disease progression is beneficial. Similarly, several studies showed that treatment with corticosteroids was associated with stable to improved LVEF in patients with preserved LV function whereas response to therapy was not as good in patients with impaired LV function(53, 108, 109). In a study evaluating the prognostic determinants of long-term survival in Japanese CS patients treated with prednisone, Yazaki and colleagues(23) found that

starting corticosteroids early prior to the occurrence of systolic dysfunction resulted in the best clinical outcomes. The 10-year survival rate for CS patients with LVEF > 50% was 89% as compared to only 27% in those with LVEF < 50%(23).

Padala and colleagues(46) retrospectively evaluated the impact of early initiation of corticosteroid therapy (within one month of CS diagnosis) on cardiac function, ventricular arrhythmias and atrioventricular (AV) block in 30 patients with CS and found that early initiation of therapy was associated with improved outcomes. Of 14 patients with reduced LVEF, 9 patients received corticosteroids within one month of CS diagnosis and they all had improved LVEF, whereas the 5 patients who had a delay in initiation of corticosteroids had no improvement in LVEF(46). Similarly, for patients who presented with ventricular arrythmia (VA) or complete heart block (CHB), 72% (8/11) did not have recurrent arrythmia and there was complete resolution of CHB in 2/3 (67%) of patients who received corticosteroid therapy within one month of CS diagnosis(46). Patients with VA or advanced AVB who failed to receive corticosteroids within one month of CS diagnosis did not show any improvement in arrythmias or in their conduction block(46).

The ERS guidelines(2) acknowledge the potential benefit of early initiation of immunosuppressive therapy in CS patients but do not prescribe a time during which therapy should be initiated. For patients who require device implantation, the Heart Rhythm Society (HRS) consensus statement(6) suggests that immunosuppression should be started after device implantation as soon as the wound is healed.

*IV. What is the optimal initial prednisone dose in CS?*

Determining the optimal initial prednisone dose for CS patients that would benefit from IST remains a challenge.

Yazaki and colleagues(23) evaluated 75 corticosteroid treated CS patients and found that there was no significant difference in survival outcomes in CS patients treated with a high initial dose of prednisone (> 40mg per day) as compared to those treated with a low initial dose (< 30mg per day)(23). In that study, patients treated with steroids (regardless of dose) had favorable clinical outcomes and a 5-year survival rate of 75% vs. 10% in those not treated with steroids(23). Prolonged and high corticosteroid doses are associated with significant morbidity and reduced quality of life in sarcoidosis patients and should be avoided where possible (110-112).

Most experts endorse a starting prednisone dose of 0.5mg/Kg up to a maximum dose between 30mg to 40mg per day with subsequent taper to the lowest most effective dose (goal 10mg/day or less)(2, 87).

The JCS guidelines(7) recommends to initiate corticosteroid therapy in CS patients with 30mg per day (0.5mg/kg daily) oral prednisone or prednisone equivalent, or 60mg every other day (1mg/Kg every other day) for the first four weeks followed by a 5mg daily (or 10 mg every other day) dose reduction at intervals of 2 to 4 weeks to a goal maintenance dose of 5 to 10 mg daily or 10 to 20 mg every other day(7). This recommendation is based on reports from expert committees but is in line with common practice and findings from the study by Yazaki and colleagues(23, 113).

*V. Use of prednisone PLUS methotrexate (or other cytotoxic) as initial therapy in CS?*

Current treatment algorithms recommend a stepwise approach to initiating therapy with prednisone and steroid sparing therapy in CS patients(2, 7). More recently however, several studies suggest that patients treated with prednisone in addition to other IST at diagnosis have better outcomes than patients treated with prednisone alone(3, 4).

Ballul and colleagues(3) retrospectively evaluated 36 patients with symptomatic CS for whom therapy was initiated with corticosteroids alone (n=24) or with combined corticosteroids and other IST (n=12), and found that over a median follow-up period of 3.6 years (range 1 – 15 years), the relapse rate was significantly higher in the corticosteroid only group in comparison to the combination therapy group (46% vs. 17%, p= 0.048). Furthermore, CS patients initiated on corticosteroid monotherapy showed a trend to a higher relapse rate whether or not other IST were subsequently added (HR 2.96%, CI 0.66-13.48, p = 0.141)(3).

In a smaller open-label study, Nagai and colleagues(72) found that CS patients who received a combined regimen of low dose prednisone (5-15mg/day) and low dose methotrexate (6mg/week) as initial treatment following CS diagnosis were

more likely to have an improved and stable LVEF (and lower serum pro brain natriuretic peptide (pro-BNP) levels) at 3- and 5-years post diagnosis(72); while patients who received initial corticosteroid monotherapy (30-60mg/day) had a decline in LVEF (and higher pro-BNP levels) by year 3 and 5 after an initial improvement in the first year(72). There was no significant difference in the observed rate of infections or other significant complications in patients treated with combined prednisone and other IST vs. prednisone only as initial therapy(3, 72).

Studies evaluating this approach are ongoing. The Cardiac Sarcoidosis Multi-Center Randomized Controlled Trial (CHASM CS-RCT) is an ongoing multicenter randomized controlled noninferiority trial designed to evaluate the optimal initial treatment strategy for patients with active CS(5). The study aims to enroll 200 CS patients randomized 1:1 to an initial treatment strategy of prednisone monotherapy (0.5 mg/kg/day for 6 months (maximum dose 30 mg daily)) or to combination therapy (prednisone 20 mg daily for 1 month, then 10 mg daily for 1 month, then 5 mg daily for one month then stop AND methotrexate 15-20 mg once weekly for 6 months)(5). 22 centers across four countries (Canada, USA, Japan, and the United Kingdom) are involved in this trial and results are expected in 2024.

*VI. What is the role of intravenous pulse dose methylprednisolone in CS?*

Intravenous (IV) methylprednisolone given as a high dose pulse therapy (500mg to 1000mg per day) for 1- to 3-days has been used in CS patients with life threatening disease manifestations with some benefit(24, 114-116). Data in support of this is limited to case reports and small case series(24, 114-116). In one small series, Slivnick and colleagues(115) describe the use of high dose IV methylprednisolone (500mg to 1000 mg daily for three days) in three patients with CS who presented with VT storm and evidence of active myocarditis as demonstrated on cardiac MRI or cardiac $^{18}$F-FDG PET scan. In all the cases, the VT storm was refractory to usual anti-arrhythmic drugs and usual dose oral corticosteroids, but responded to high dose IV prednisolone within 24 to 48 hours of initiation of therapy(115). Similar responses were observed in other case reports(24, 114, 116).

The rationale for high dose IV-glucocorticoids is that it has more rapid onset of action and greater lymphocyte inhibition compared with lower dosages(117). Furthermore, high dose IV-glucocorticoids appear to be effective for acute life-threatening manifestations of other autoimmune diseases(117-119). High dose IV-glucocorticoids have been associated with an increased risk of infection and lower pulse dose corticosteroid therapy has been used(118, 119). A recent prospective study by Kafil and colleagues(120) reported on 5 patients with CS and VT storm who were successfully treated with an initial dose of IV methylprednisolone given as 40 mg daily or twice daily followed by oral prednisone 40 mg daily for a minimum of 6-months with subsequent slow taper(120). In their study, all the patients had complete resolution of their arrythmia after 2 doses of IV methylprednisolone and remained free of VT storm after 1-year(120). The median duration of IV therapy was 2-days with a range of 2 to 5-days(120).

Neither the JCS(7) nor the HRS(6) guidelines make any recommendations for or against the use of pulse dose IV methylprednisolone in patients with CS. The recently published ERS guidelines(2) note that there is insufficient data to determine if pulse dose IV methylprednisolone is useful and add that it is unclear for whom it should be considered. Based on the limited data above, it may be a viable treatment option for CS patients presenting with VT storm refractory to usual dose oral steroids.

*VII. What is the role of Infliximab and other anti-TNF Agents in CS?*

Infliximab and adalimumab(70, 121-125) have been used with good outcomes in patients with other forms of severe pulmonary and extracardiac sarcoidosis refractory to (or intolerant of) corticosteroids and second-line steroid sparing therapy(1, 2). Although they have been used in CS patients with some reported benefit, wide acceptance of these agents has been limited by concerns about cardiotoxicity and an FDA Blackbox warning about use in patients with heart failure(12, 126, 127). The ERS guidelines(2) note that anti-TNF agents may be useful for the treatment of CS in patient's refractory to, or intolerant of steroids and other IST (refractory CS), however, there was insufficient evidence to make a strong guideline recommendation.

### Infliximab

Infliximab is an intravenously administered mouse/human chimeric immunoglobulin G (IgG) monoclonal antibody directed against TNF-α which is the principal cytokine mediating the formation, persistence, and expansion of the sarcoid granuloma(128-130). It is the best studied and the most widely used biologic agent in sarcoidosis(128).

Data in support of the use of infliximab in CS is based on several observational studies(11, 12, 51, 121, 125, 131-135) and a randomized controlled study with a small subset of CS patients(136). Judson and colleagues(136) published data from a randomized placebo-controlled trial of infliximab (3mg/Kg and 5mg/Kg body weight) in patients with extrapulmonary sarcoidosis. That study included 138 patients, 12 (9%) of whom had CS and found that compared to placebo, infliximab was beneficial in the treatment of extrapulmonary sarcoidosis (including CS) in patients already receiving corticosteroids(136). Four of the 8 CS patients assigned to active drug treatment had resolution of disease while none of the 4 patients assigned to placebo had disease resolution after 6-months of therapy(136). Bakker and colleagues(11) retrospectively evaluated 22 patients with active CS refractory to (n=19) or intolerant of (n=3) steroids/IST who received infliximab (5mg/kg at week 0, 2, and subsequently every 4 weeks) for at least 6-months, and found that majority of the patients (18/22; 82%) responded to therapy. Response to therapy was defined as any one of: reduction in dose of concomitant immunosuppressive therapy, 10% improvement in LVEF, 25% reduction in myocardial SUVmax or improvement in NYHA functional status by at least one class(11). Overall, the median LVEF in study subjects improved from 45% to 55% (p=0.02)(11). Harper and colleagues(12) also observed that 67% (24/36) of CS patients treated with infliximab responded to therapy in at least one of three outcome categories (decrease in daily corticosteroid dose of ≥10 mg, improvement in dysrhythmia or improvement of LVEF by >5%). The median (IQR) LVEF at study entry was 41% (32% – 55%) and this was unchanged after 6-months of therapy(12).

Data from the anti-TNF therapy against congestive heart failure (ATTACH) trial(126) showed an increased risk of death and hospitalization in patients with LVEF <= 35% and NYHA class III to IV symptoms treated with high dose infliximab (10 mg/Kg)(126). The implications of this finding in CS patients are unclear since most of the patients enrolled in the ATTACH trial had ischemic and non-inflammatory cardiomyopathy(126). Following the ATTACH trial, several studies have been published suggesting that infliximab (given at doses of 3mg/kg or 5mg/Kg) is safe in CS patients with moderate to severe heart failure(11, 12, 137). For example, the median LVEF in the study by Bakker and colleagues was 47.5% albeit 7 patients (32%) had LVEF < 35%(11). No patient in that study had worsening heart failure, and the median LVEF increased from 45% to 55%(11). Similarly, Harper and colleagues(12) enrolled 36 patients (median LVEF of 41%), 6 (17%) of whom had LVEF < 30% and only 1 patient (LVEF 27%) who also had > 50% myocardial involvement on cardiac PET had worsening heart failure requiring heart transplantation. Patients in both studies received infliximab infusions for a minimum of 6-months(11, 12).

Although infliximab is generally well tolerated, it has been associated with an increased risk of adverse events, particularly infections(11, 12, 131, 138). Maneiro and colleagues(139) published a systematic review that included 232 sarcoidosis patients (69 studies) treated with infliximab, and found that the mean weighted rate of adverse events in sarcoidosis patients treated with infliximab was 39.9 per 100 patient-years. This included rates of 22.1, 5.9 and 1.0 per 100 patient-years for patients who developed infections, serious infections and malignancy(139). In one of the largest studies that enrolled CS patients treated with infliximab, Harper and colleagues(12) found that adverse events attributable to infliximab occurred in 6/36 (17%) of patients however this required discontinuation of therapy in only 3 patients (8%). Infectious complications were the most common adverse events (5/6) nevertheless most patients required no interruption or only a temporary delay in the subsequent dose(12). Chapelon-Abric and colleagues(131) found that male gender and more prolonged use of steroids and other IST prior to initiation of infliximab was associated with a higher risk of infectious complications in sarcoidosis patients treated with infliximab.

Practice guidelines for the use of infliximab in patients with sarcoidosis have been published(140). They recommend consideration of infliximab in patients with refractory CS who do not have NYHA

class III/IV symptoms(140). For patients with refractory CS and NYHA class III/IV heart failure symptoms, the guidelines endorse caution but emphasize the need to individualize therapy(140). Patients with CS as the only known cause of heart failure should be considered for infliximab, however, if besides CS other causes of heart failure are present, infliximab should be considered contraindicated(140). Many experts recommend that a cardiac PET scan be performed prior to starting infliximab. If there is evidence of significant cardiac inflammation based on cardiac PET scan, then infliximab can be considered.

Table 7 summarizes the practice guidelines for infliximab as it affects CS patients(140). The recommended starting dose of infliximab is 5mg/Kg given as an initial loading dose at week 0 and 2, followed by a maintenance dose of 5mg/kg every four- to six-weeks(140). To prevent anti-drug antibody formation, anti-TNF therapy should be combined with low dose methotrexate and/or glucocorticoids(140). Presence of active or latent TB, as well as other forms of serious bacterial or fungal infections should be excluded prior to starting anti-TNF therapy(140). Anti-TNF therapy should be avoided if there is any evidence of active herpes zoster infection, active hepatitis B or C infection, presence of active or prior malignancy in the preceding 5 years, and at least 2 to 3 months prior to planned pregnancy, during pregnancy or if breast feeding(140). Table 7 summarizes what immunizations to give or avoid in sarcoidosis patients on infliximab and how to taper and discontinue therapy(140, 141).

**Table 7.** Anti TNF antagonists in Cardiac Sarcoidosis(140)

| **Anti-TNF Agent** | **Infliximab** | **Adalimumab** |
|---|---|---|
| **Route** | Intravenous (IV) | Subcutaneous (SQ) |
| **Dose** | 5mg/Kg body weight IV; Give loading dose at week 0 and 2, followed by a maintenance dose of 5mg/kg body weight every 4- to 6-weeks. | 80-160 mg SQ at week 0, 40 mg at week 1, and 40 mg once every week thereafter. |
| **Discontinuation of Therapy** | Maintain the same dosage and gradually prolong the interval between 2 doses to 5 weeks (for 3 doses), 6 weeks (for 3 doses), 8 weeks (for 3 doses), 12 weeks (for 3 doses) and stop. | Continue dosage unchanged and prolong the interval between 2 doses to once in every 10 days (for 3 months), once in every 2 weeks (for 3 months), and then stop. |
| **Indications** | 1. Refractory CS without NYHA Class III/IV symptoms<br>2. Consider use in patients with NYHA III/IV symptoms if CS is the only known cause of HF.<br>3. Avoid use in NYHA III/IV symptoms if other etiology of HF (other than CS) cannot be excluded. | |
| **Contraindications** | Infections:<br>- Active or latent TB infection<br>- Opportunistic infection<br>- Serious bacterial or fungal infections<br>- Active herpes zoster infection<br>- Active hepatitis B or C infection<br>Malignancy<br>- Presence of active or prior malignancy in the preceding 5 years.<br>Pregnancy and Breast Feeding<br>- Avoid during pregnancy, planned pregnancy (for at least 2 to 3-months prior) or if breastfeeding.<br>*Decompensated HF with NYHA III/IV symptoms not due to cardiac sarcoidosis is contraindication | |
| **Pre-initiation testing** | IGRA test, Hepatitis B and C serology, HIV serology, rule out any URTI, recent antibiotic use or other active infection. | |
| **Prevention of anti-drug antibody** | Low dose methotrexate and/or glucocorticoids | |
| **Vaccinations** | 1. Avoid live, attenuated vaccines.<br>2. Encourage preventive influenza, pneumococcal and hepatitis B vaccination before or during therapy with TNF inhibitors.<br>3. Encourage the COVID-19 3-dose vaccination series | |
| **Duration of Therapy** | Treat for at least 3 to 6 months prior to determining efficacy. Consider stable dose for 6 to 12-months after sustained response prior to discontinuing or tapering therapy. | |

Key: NYHA = New York Heart Association, HF = heart Failure, IV = intravenous, SQ = subcutaneous' * Consider use in patients with NYHA III/IV symptoms if CS is the only known cause of HF.

**Table 8.** Predictors of Response to Infliximab in Patients with other forms of Sarcoidosis(128, 142-144)

| |
|---|
| Evidence of active Inflammation |
| - Elevated CRP |
| - Elevated serum soluble IL-2 receptor levels |
| - Elevated SUV max on PET Scanning |
| Genetic |
| - TNF-308A polymorphisms* |
| CD4+ Lymphopenia |
| Concomitant prednisone dose ** |

* TNF-308A GG-genotype had a three-fold higher response to anti-TNF agents than did patients with the AA or AG genotypes(142); **There was no additional benefit of infliximab in patients on high prednisone doses (> 15mg/day)(143)

Infliximab is expensive and most insurance companies do not readily approve its use. Predictors of response to infliximab in CS are unknown. Table 8 summarizes the predictors of response to infliximab in patients with pulmonary sarcoidosis, however it is unknown if these are applicable to patients with CS.

### Adalimumab

Adalimumab is a recombinant non-chimeric human IgG1 monoclonal antibody directed against human TNF. Like Infliximab, it has high affinity and specificity for soluble TNF-α, but not to TNF-β(128). Unlike infliximab, it is given subcutaneously (SQ) and can be self-administered(128). As a non-chimeric monoclonal antibody, it has less risk of antidrug antibodies and may be better tolerated (121, 145).

Data in support of the use of adalimumab in CS is limited to retrospective studies and case reports (121-124). Rosenthal and colleagues (124) retrospectively evaluated 28 patients with CS and found that 16/19 (84%) patients who received adalimumab for refractory CS or intolerance to methotrexate had improvement in myocardial $^{18}$F-FDG uptake; and 12 of these (63%) had complete resolution of myocardial $^{18}$F-FDG uptake. Refractory CS was defined in this study as presence of persistently active disease (by myocardial $^{18}$F-FDG uptake) despite treatment with high dose prednisone (> 30 mg/day for 4 to 8 weeks with subsequent taper to 5mg/day) and methotrexate (initiated at 10 to 15mg/week and up titrated by 5mg every 2-weeks to goal dose of 20mg weekly)(124). Adalimumab was given at a dose of 40 mg SQ every other week in combination with methotrexate 15mg weekly in this study(124).

Jamilloux and colleagues(121) published a large retrospective multicenter study that included 132 patients with sarcoidosis and found that CS patients (n=28) treated with either Infliximab or Adalimumab had a significant improvement in the ePOST (extrapulmonary Physician Organ Severity Tool) score. There was no significant difference in response between these TNF antagonists however, severe allergic reactions were more common in patients taking infliximab than those on adalimumab(121). Adalimumab has been safely used in patients allergic to, or otherwise intolerant to infliximab(121, 146-148).

The usual dose of adalimumab in sarcoidosis is 40 mg SQ every 1 to 2 weeks (Table 7)(2, 140). Most experienced sarcoidosis experts favor weekly dosing as this may be associated with better response rates(140, 149). As with infliximab, it is recommended to give adalimumab in combination with low dose prednisone or methotrexate to reduce the incidence of serum antibody formation(140, 149). These serum antibodies are associated with lower serum drug concentrations and non-response to therapy(140, 149, 150).

Adalimumab is contraindicated in patients with severe congestive heart failure, prior or active malignancy, demyelinating neurologic disease and deep fungal infections (Table 7)(2). As with infliximab, it is important to monitor for infections in patients on adalimumab, and to screen for tuberculosis prior to initiating therapy (2, 140). Although the incidence of Pneumocystis jiroveci Pneumonia (PJP) infection in patients with sarcoidosis is low, it is recommended that sarcoidosis patients on anti-TNF therapy be considered for PJP prophylaxis(141).

## *VIII. What other Immunomodulators have been used in CS?*

### Rituximab

Rituximab is an intravenous mouse/human chimeric IgG kappa monoclonal antibody directed

against CD20 antigen preferentially found on the surface of mature peripheral (but not hematopoietic stem cells) B-lymphocytes(151, 152). Rituximab works by binding to the CD20 receptor on the surface of B-lymphocytes and inducing cell death in a variety of direct and indirect mechanisms(152). Following infusion of Rituximab, there is complete B-cell depletion and lymphopenia typically lasting 6-months, however because hematopoietic stem cells are spared, there is usually full recovery of B-lymphocytes in the peripheral blood within 9 to 12 months(151).

Data in support of the use of rituximab in CS is limited to case reports and retrospective reviews and suggest that rituximab may be beneficial in CS patients presenting with both heart failure and life-threatening arrhythmias(153, 154). Elwazir and colleagues(154) evaluated 7-patients with active CS refractory to (or intolerant of) steroids and other IST who were treated with rituximab and 6/7 (86%) patients had improvement in myocardial $^{18}$F-FDG uptake while 5/7 patients had improved arrythmia burden (on Holter monitoring or ICD interrogation)(154). There was no significant change in the mean LVEF before and after treatment(154). Patients received rituximab 1000 mg intravenously as 2 doses separated by 2 weeks, with repeat dosing given at 6-monthly intervals in patients who had persistent myocardial 18F-FDG uptake or recurrent symptoms (arrythmias, high grade AVB)(154). Most patients tolerated the infusion well, however one patient developed fungal catheter-associated infection and sepsis requiring discontinuation of rituximab(154). Most patients received multiple rounds of rituximab; up to 8 rounds in one patient with no adverse events reported(154).

Rituximab has been associated with a lower rate of drug failure than anti-TNF agents(155). A retrospective study by Lower and colleagues evaluated 317 patients with sarcoidosis treated with infliximab, adalimumab or rituximab and found that the rate of discontinuation of drug therapy was highest for adalimumab (58%) and lowest for rituximab (29%)(155). Patients were more likely to discontinue infliximab and adalimumab for infections and allergic reactions, than they were to discontinue rituximab(155).

The most recent ERS guidelines list rituximab as a potential 3rd line agent that may be useful in CS; but does not make any recommendations for or against its use(2). Rituximab carries a high risk for reactivation of viral infections, and patients should be screened for viral hepatitis prior to initiating therapy (Table 7)(2). Rituximab can also lead to IgG deficiency therefore it is important to monitor IgG levels with chronic therapy(2). Monitoring for infections is also strongly recommended(2).

### *IX. Algorithmic Approach to treatment of CS*

Figure 1 reproduced with permission from the ERS guidelines(2) outlines the current approach to the use of immunosuppressive therapy in CS.

This approach represents a combination of recommendations made in the guidelines as well as a description of current practices where there was insufficient evidence to make a recommendation(2). It considers the concomitant initiation of corticosteroids and IST consistent with recent information suggesting outcomes maybe better with that approach(3, 72).

### *X. Duration of Immunosuppression in CS*

There is no guidance on the duration of IST in CS patients, however there is suggestion that long term treatment may be warranted(48, 124, 156).

Nagai and colleagues(156) retrospectively evaluated 61 CS patients during a mean follow-up period of 10 years and found that discontinuation of therapy was associated with decreased LVEF (following an initial improvement on therapy), and higher cardiac mortality compared to continuation of therapy(156). Another study by Rosenthal and colleagues(124) showed similar findings. 8 of 9 patients (89%) who discontinued immunosuppression after achieving initial complete resolution of cardiac inflammation (on PET scan) had radiographic CS recurrence an average of 8.4 months after discontinuation of therapy compared to 3/19 (16%) of patients with uninterrupted immunosuppression(124). The mean duration of therapy (prior to discontinuation) was 32 months(124). These data suggest that prolonged and perhaps indefinite immunosuppression may be beneficial for CS patients(124, 156) and, for patients who stop immunosuppression, close surveillance with serial cardiac PET scans may be beneficial(124).

## Conclusion

CS remains one of the most severe forms of sarcoidosis, yet several aspects of care remain unclear. Patients presenting with functional cardiac abnormalities, including heart blocks, dysrhythmias, or cardiomyopathy are at an increased risk of adverse outcomes and should be strongly considered for immunosuppressive therapy(2). While Prednisone and other immunosuppressive therapy have been shown to be beneficial in CS patients, there is a suggestion that outcomes may be improved by concomitant initiation of therapy and studies are ongoing to better answer this question(3-5). Prolonged and high corticosteroid doses are associated with significant morbidity(110-112) and there is data to show that initial prednisone doses higher than 30mg to 40mg daily are not necessary in CS patients(23). Therapy should be initiated early during disease and prolonged duration is often required(46, 48, 124, 156). TNF blockers have been safely used in CS patients including in those with low LVEF(11, 12, 121), however their role in CS needs to be better clarified.

**Conflicts of interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

## References

1. Rahaghi FF, Baughman RP, Saketkoo LA, Sweiss NJ, Barney JB, Birring SS, et al. Delphi consensus recommendations for a treatment algorithm in pulmonary sarcoidosis. Eur Respir Rev. 2020;29(155). Epub 2020/03/20. doi: 10.1183/16000617.0146-2019. PubMed PMID: 32198218.
2. Baughman RP, Valeyre D, Korsten P, Mathioudakis AG, Wuyts WA, Wells A, et al. ERS clinical practice guidelines on treatment of sarcoidosis. Eur Respir J. 2021;58(6). Epub 2021/06/19. doi: 10.1183/13993003.04079-2020. PubMed PMID: 34140301.
3. Ballul T, Borie R, Crestani B, Daugas E, Descamps V, Dieude P, et al. Treatment of cardiac sarcoidosis: A comparative study of steroids and steroids plus immunosuppressive drugs. Int J Cardiol. 2019;276:208-11. Epub 2018/11/30. doi: 10.1016/j.ijcard.2018.11.131. PubMed PMID: 30527995.
4. Stievenart J, Le Guenno G, Ruivard M, Rieu V, Andre M, Grobost V. Cardiac sarcoidosis: systematic review of literature on corticosteroid and immunosuppressive therapies. Eur Respir J. 2021. Epub 2021/09/18. doi: 10.1183/13993003.00449-2021. PubMed PMID: 34531273.
5. Birnie D, Beanlands RSB, Nery P, Aaron SD, Culver DA, DeKemp RA, et al. Cardiac Sarcoidosis multi-center randomized controlled trial (CHASM CS- RCT). Am Heart J. 2020;220:246-52. Epub 2019/10/20. doi: 10.1016/j.ahj.2019.10.003. PubMed PMID: 31911261; PubMed Central PMCID: PMC7367280.
6. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. Heart Rhythm. 2014;11(7):1305-23. Epub 2014/05/14. doi: 10.1016/j.hrthm.2014.03.043. PubMed PMID: 24819193.
7. Terasaki F, Azuma A, Anzai T, Ishizaka N, Ishida Y, Isobe M, et al. JCS 2016 Guideline on Diagnosis and Treatment of Cardiac Sarcoidosis - Digest Version. Circ J. 2019;83(11):2329-88. Epub 2019/10/09. doi: 10.1253/circj.CJ-19-0508. PubMed PMID: 31597819.
8. Fussner LA, Karlstedt E, Hodge DO, Fine NM, Kalra S, Carmona EM, et al. Management and outcomes of cardiac sarcoidosis: a 20-year experience in two tertiary care centres. Eur J Heart Fail. 2018;20(12):1713-20. Epub 2018/10/31. doi: 10.1002/ejhf.1319. PubMed PMID: 30378224.
9. Zhou Y, Lower EE, Li HP, Costea A, Attari M, Baughman RP. Cardiac Sarcoidosis: The Impact of Age and Implanted Devices on Survival. Chest. 2017;151(1):139-48. Epub 2016/09/08. doi: 10.1016/j.chest.2016.08.1457. PubMed PMID: 27614001.
10. West SG. Current management of sarcoidosis I: pulmonary, cardiac, and neurologic manifestations. Curr Opin Rheumatol. 2018;30(3):243-8. doi: 10.1097/BOR.0000000000000489. PubMed PMID: 29389828.
11. Bakker ALM, Mathijssen H, Azzahhafi J, Swaans MJ, Veltkamp M, Keijsers RGM, et al. Effectiveness and safety of infliximab in cardiac Sarcoidosis. Int J Cardiol. 2021;330:179-85. Epub 2021/02/15. doi: 10.1016/j.ijcard.2021.02.022. PubMed PMID: 33582196.
12. Harper LJ, McCarthy M, Ribeiro Neto ML, Hachamovitch R, Pearson K, Bonanno B, et al. Infliximab for Refractory Cardiac Sarcoidosis. Am J Cardiol. 2019;124(10):1630-5. Epub 2019/08/23. doi: 10.1016/j.amjcard.2019.07.067. PubMed PMID: 31500815.
13. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35. Epub 2013/04/11. doi: 10.1016/j.jclinepi.2013.02.003. PubMed PMID: 23570745.
14. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. Circulation. 1978;58(6):1204-11. doi: 10.1161/01.cir.58.6.1204. PubMed PMID: 709777.
15. Iwai K, Sekiguti M, Hosoda Y, DeRemee RA, Tazelaar HD, Sharma OP, et al. Racial difference in cardiac sarcoidosis incidence observed at autopsy. Sarcoidosis. 1994;11(1):26-31. PubMed PMID: 8036339.
16. Hu X, Carmona EM, Yi ES, Pellikka PA, Ryu J. Causes of death in patients with chronic sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2016;33(3):275-80. PubMed PMID: 27758994.
17. Sekiguchi M, Hiroe M, Take M, Hirosawa K. Clinical and histopathological profile of sarcoidosis of the heart and acute idiopathic myocarditis. Concepts through a study employing endomyocardial biopsy. II. Myocarditis. Jpn Circ J. 1980;44(4):264-73. PubMed PMID: 6154812.
18. Takaya Y, Kusano KF, Nakamura K, Ito H. Outcomes in patients with high-degree atrioventricular block as the initial manifestation of cardiac sarcoidosis. Am J Cardiol. 2015;115(4):505-9. Epub 2014/11/29. doi: 10.1016/j.amjcard.2014.11.028. PubMed PMID: 25529542.
19. Ekström K, Lehtonen J, Nordenswan HK, Mäyränpää MI, Räisänen-Sokolowski A, Kandolin R, et al. Sudden death in cardiac sarcoidosis: an analysis of nationwide clinical and cause-of-death registries. Eur Heart J. 2019. Epub 2019/06/23. doi: 10.1093/eurheartj/ehz428. PubMed PMID: 31230070.
20. Nordenswan HK, Lehtonen J, Ekström K, Kandolin R, Simonen P, Mäyränpää M, et al. Outcome of Cardiac Sarcoidosis Presenting With High-Grade Atrioventricular Block. Circ Arrhythm Electrophysiol.

2018;11(8):e006145. doi: 10.1161/CIRCEP.117.006145. PubMed PMID: 30354309.
21. Cacoub P, Chapelon-Abric C, Resche-Rigon M, Saadoun D, Desbois AC, Biard L. Cardiac sarcoidosis: A long term follow up study. PLoS One. 2020;15(9):e0238391. Epub 2020/09/19. doi: 10.1371/journal.pone.0238391. PubMed PMID: 32946452; PubMed Central PMCID: PMC7500618.
22. Kandolin R, Lehtonen J, Kupari M. Cardiac sarcoidosis and giant cell myocarditis as causes of atrioventricular block in young and middle-aged adults. Circ Arrhythm Electrophysiol. 2011;4(3):303-9. Epub 2011/03/22. doi: 10.1161/CIRCEP.110.959254. PubMed PMID: 21427276.
23. Yazaki Y, Isobe M, Hiroe M, Morimoto S, Hiramitsu S, Nakano T, et al. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. Am J Cardiol. 2001;88(9):1006-10. PubMed PMID: 11703997.
24. Chapelon-Abric C, de Zuttere D, Duhaut P, Veyssier P, Wechsler B, Huong DL, et al. Cardiac sarcoidosis: a retrospective study of 41 cases. Medicine (Baltimore). 2004;83(6):315-34. doi: 10.1097/01.md.0000145367.17934.75. PubMed PMID: 15525844.
25. Rosenthal DG, Cheng RK, Petek BJ, Masri SC, Mikacenic C, Raghu G, et al. Risk of Adverse Cardiovascular Events in Cardiac Sarcoidosis Independent of Left Ventricular Function. Am J Cardiol. 2020;127:142-8. Epub 2020/04/23. doi: 10.1016/j.amjcard.2020.04.025. PubMed PMID: 32402485.
26. Blankstein R, Osborne M, Naya M, Waller A, Kim CK, Murthy VL, et al. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. J Am Coll Cardiol. 2014;63(4):329-36. Epub 2013/10/16. doi: 10.1016/j.jacc.2013.09.022. PubMed PMID: 24140661; PubMed Central PMCID: PMC3955730.
27. Flores RJ, Flaherty KR, Jin Z, Bokhari S. The prognostic value of quantitating and localizing F-18 FDG uptake in cardiac sarcoidosis. J Nucl Cardiol. 2018. Epub 2018/11/12. doi: 10.1007/s12350-018-01504-y. PubMed PMID: 30421379.
28. Sperry BW, Tamarappoo BK, Oldan JD, Javed O, Culver DA, Brunken R, et al. Prognostic Impact of Extent, Severity, and Heterogeneity of Abnormalities on. JACC Cardiovasc Imaging. 2018;11(2 Pt 2):336-45. Epub 2017/08/16. doi: 10.1016/j.jcmg.2017.04.020. PubMed PMID: 28823747.
29. Ise T, Hasegawa T, Morita Y, Yamada N, Funada A, Takahama H, et al. Extensive late gadolinium enhancement on cardiovascular magnetic resonance predicts adverse outcomes and lack of improvement in LV function after steroid therapy in cardiac sarcoidosis. Heart. 2014;100(15):1165-72. Epub 2014/05/14. doi: 10.1136/heartjnl-2013-305187. PubMed PMID: 24829369.
30. Hulten E, Agarwal V, Cahill M, Cole G, Vita T, Parrish S, et al. Presence of Late Gadolinium Enhancement by Cardiac Magnetic Resonance Among Patients With Suspected Cardiac Sarcoidosis Is Associated With Adverse Cardiovascular Prognosis: A Systematic Review and Meta-Analysis. Circ Cardiovasc Imaging. 2016;9(9):e005001. doi: 10.1161/CIRCIMAGING.116.005001. PubMed PMID: 27621357; PubMed Central PMCID: PMC5449111.
31. Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, Ylitalo K, et al. Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. Circulation. 2015;131(7):624-32. Epub 2014/12/19. doi: 10.1161/CIRCULATIONAHA.114.011522. PubMed PMID: 25527698.
32. Joyce E, Ninaber MK, Katsanos S, Debonnaire P, Kamperidis V, Bax JJ, et al. Subclinical left ventricular dysfunction by echocardiographic speckle-tracking strain analysis relates to outcome in sarcoidosis. Eur J Heart Fail. 2015;17(1):51-62. Epub 2014/11/29. doi: 10.1002/ejhf.205. PubMed PMID: 25431267.
33. Kandolin R, Lehtonen J, Airaksinen J, Vihinen T, Miettinen H, Kaikkonen K, et al. Usefulness of Cardiac Troponins as Markers of Early Treatment Response in Cardiac Sarcoidosis. Am J Cardiol. 2015;116(6):960-4. Epub 2015/06/26. doi: 10.1016/j.amjcard.2015.06.021. PubMed PMID: 26209113.
34. Yoshida Y, Morimoto S, Hiramitsu S, Tsuboi N, Hirayama H, Itoh T. Incidence of cardiac sarcoidosis in Japanese patients with high-degree atrioventricular block. Am Heart J. 1997;134(3):382-6. PubMed PMID: 9327691.
35. Fawcett FJ, Goldberg MJ. Heart block resulting from myocardial sarcoidosis. Br Heart J. 1974;36(2):220-3. doi: 10.1136/hrt.36.2.220. PubMed PMID: 4818154; PubMed Central PMCID: PMC458821.
36. Roberts WC, McAllister HA, Ferrans VJ. Sarcoidosis of the heart. A clinicopathologic study of 35 necropsy patients (group 1) and review of 78 previously described necropsy patients (group 11). Am J Med. 1977;63(1):86-108. doi: 10.1016/0002-9343(77)90121-8. PubMed PMID: 327806.
37. Nery PB, Beanlands RS, Nair GM, Green M, Yang J, McArdle BA, et al. Atrioventricular block as the initial manifestation of cardiac sarcoidosis in middle-aged adults. J Cardiovasc Electrophysiol. 2014;25(8):875-81. Epub 2014/05/02. doi: 10.1111/jce.12401. PubMed PMID: 24602015.
38. Fazelpour S, Sadek MM, Nery PB, Beanlands RS, Tzemos N, Toma M, et al. Corticosteroid and Immunosuppressant Therapy for Cardiac Sarcoidosis: A Systematic Review. J Am Heart Assoc. 2021;10(17):e021183. Epub 2021/09/03. doi: 10.1161/JAHA.121.021183. PubMed PMID: 34472360.
39. Sadek MM, Yung D, Birnie DH, Beanlands RS, Nery PB. Corticosteroid therapy for cardiac sarcoidosis: a systematic review. Can J Cardiol. 2013;29(9):1034-41. Epub 2013/04/30. doi: 10.1016/j.cjca.2013.02.004. PubMed PMID: 23623644.
40. Chapelon-Abric C, Sene D, Saadoun D, Cluzel P, Vignaux O, Costedoat-Chalumeau N, et al. Cardiac sarcoidosis: Diagnosis, therapeutic management and prognostic factors. Arch Cardiovasc Dis. 2017;110(8-9):456-65. doi: 10.1016/j.acvd.2016.12.014. PubMed PMID: 28566197.
41. Banba K, Kusano KF, Nakamura K, Morita H, Ogawa A, Ohtsuka F, et al. Relationship between arrhythmogenesis and disease activity in cardiac sarcoidosis. Heart Rhythm. 2007;4(10):1292-9. Epub 2007/06/16. doi: 10.1016/j.hrthm.2007.06.006. PubMed PMID: 17905334.
42. Yodogawa K, Seino Y, Shiomura R, Takahashi K, Tsuboi I, Uetake S, et al. Recovery of atrioventricular block following steroid therapy in patients with cardiac sarcoidosis. J Cardiol. 2013;62(5):320-5. Epub 2013/09/06. doi: 10.1016/j.jjcc.2013.07.007. PubMed PMID: 24016620.
43. Orii M, Tanimoto T, Ota S, Takagi H, Tanaka R, Fujiwara J, et al. Diagnostic accuracy of cardiac magnetic resonance imaging for cardiac sarcoidosis in complete heart block patients implanted with magnetic resonance-conditional pacemaker. J Cardiol. 2020;76(2):191-7. Epub 2020/03/14. doi: 10.1016/j.jjcc.2020.02.014. PubMed PMID: 32184028.
44. Chiu CZ, Nakatani S, Zhang G, Tachibana T, Ohmori F, Yamagishi M, et al. Prevention of left ventricular remodeling by long-term corticosteroid therapy in patients with cardiac sarcoidosis. Am J Cardiol. 2005;95(1):143-6. Epub 2004/12/28. doi: 10.1016/j.amjcard.2004.08.083. PubMed PMID: 15619415.
45. Kaida T, Inomata T, Minami Y, Yazaki M, Fujita T, Iida Y, et al. Importance of Early Diagnosis of Cardiac Sarcoidosis in Patients with Complete Atrioventricular Block. Int Heart J. 2018;59(4):772-8. Epub 2018/05/23. doi: 10.1536/ihj.17-492. PubMed PMID: 29794391.
46. Padala SK, Peaslee S, Sidhu MS, Steckman DA, Judson MA. Impact of early initiation of corticosteroid therapy on cardiac function and rhythm in patients with cardiac sarcoidosis. Int J Cardiol. 2017;227:565-70. Epub 2016/11/02. doi: 10.1016/j.ijcard.2016.10.101. PubMed PMID: 27836297.

47. Kudoh H, Fujiwara S, Shiotani H, Kawai H, Hirata K. Myocardial washout of 99mTc-tetrofosmin and response to steroid therapy in patients with cardiac sarcoidosis. Ann Nucl Med. 2010;24(5):379-85. Epub 2010/05/08. doi: 10.1007/s12149-010-0376-8. PubMed PMID: 20454875.
48. Nagai T, Nagano N, Sugano Y, Asaumi Y, Aiba T, Kanzaki H, et al. Effect of Corticosteroid Therapy on Long-Term Clinical Outcome and Left Ventricular Function in Patients With Cardiac Sarcoidosis. Circ J. 2015;79(7):1593-600. Epub 2015/04/16. doi: 10.1253/circj.CJ-14-1275. PubMed PMID: 25877828.
49. Nagai S, Yokomatsu T, Tanizawa K, Ikezoe K, Handa T, Ito Y, et al. Treatment with methotrexate and low-dose corticosteroids in sarcoidosis patients with cardiac lesions. Intern Med. 2014;53(5):427-33. doi: 10.2169/internalmedicine.53.0794. PubMed PMID: 24583430.
50. Takaya Y, Kusano KF, Nakamura K, Kaji M, Shinya T, Kanazawa S, et al. Reduction of myocardial inflammation with steroid is not necessarily associated with improvement in left ventricular function in patients with cardiac sarcoidosis: predictors of functional improvement. Int J Cardiol. 2014;176(2):522-5. Epub 2014/07/12. doi: 10.1016/j.ijcard.2014.07.042. PubMed PMID: 25062558.
51. Gilotra NA, Wand AL, Pillarisetty A, Devraj M, Pavlovic N, Ahmed S, et al. Clinical and Imaging Response to Tumor Necrosis Factor Alpha Inhibitors in Treatment of Cardiac Sarcoidosis: A Multicenter Experience. J Card Fail. 2021;27(1):83-91. Epub 2020/09/06. doi: 10.1016/j.cardfail.2020.08.013. PubMed PMID: 32889044; PubMed Central PMCID: PMC8350936.
52. Medor MC, Spence S, Nery PB, Beanlands R, Promislow S, Juneau D, et al. Treatment with corticosteroids is associated with an increase in ventricular arrhythmia burden in patients with clinically manifest cardiac sarcoidosis: Insights from implantable cardioverter-defibrillator diagnostics. J Cardiovasc Electrophysiol. 2020. Epub 2020/07/26. doi: 10.1111/jce.14689. PubMed PMID: 32713090.
53. Yodogawa K, Seino Y, Ohara T, Takayama H, Katoh T, Mizuno K. Effect of corticosteroid therapy on ventricular arrhythmias in patients with cardiac sarcoidosis. Ann Noninvasive Electrocardiol. 2011;16(2):140-7. doi: 10.1111/j.1542-474X.2011.00418.x. PubMed PMID: 21496164.
54. Jefic D, Joel B, Good E, Morady F, Rosman H, Knight B, et al. Role of radiofrequency catheter ablation of ventricular tachycardia in cardiac sarcoidosis: report from a multicenter registry. Heart Rhythm. 2009;6(2):189-95. Epub 2008/10/30. doi: 10.1016/j.hrthm.2008.10.039. PubMed PMID: 19187909.
55. Futamatsu H, Suzuki J, Adachi S, Okada H, Otomo K, Ohara T, et al. Utility of gallium-67 scintigraphy for evaluation of cardiac sarcoidosis with ventricular tachycardia. Int J Cardiovasc Imaging. 2006;22(3-4):443-8. Epub 2006/03/14. doi: 10.1007/s10554-005-9043-x. PubMed PMID: 16763884.
56. Yalagudri S, Zin Thu N, Devidutta S, Saggu D, Thachil A, Chennapragada S, et al. Tailored approach for management of ventricular tachycardia in cardiac sarcoidosis. J Cardiovasc Electrophysiol. 2017;28(8):893-902. doi: 10.1111/jce.13228. PubMed PMID: 28429512.
57. Naruse Y, Sekiguchi Y, Nogami A, Okada H, Yamauchi Y, Machino T, et al. Systematic treatment approach to ventricular tachycardia in cardiac sarcoidosis. Circ Arrhythm Electrophysiol. 2014;7(3):407-13. Epub 2014/05/16. doi: 10.1161/CIRCEP.113.000734. PubMed PMID: 24837644.
58. Winters SL, Cohen M, Greenberg S, Stein B, Curwin J, Pe E, et al. Sustained ventricular tachycardia associated with sarcoidosis: assessment of the underlying cardiac anatomy and the prospective utility of programmed ventricular stimulation, drug therapy and an implantable antitachycardia device. J Am Coll Cardiol. 1991;18(4):937-43. PubMed PMID: 1894867.
59. Stees CS, Khoo MS, Lowery CM, Sauer WH. Ventricular tachycardia storm successfully treated with immunosuppression and catheter ablation in a patient with cardiac sarcoidosis. J Cardiovasc Electrophysiol. 2011;22(2):210-3. doi: 10.1111/j.1540-8167.2010.01826.x. PubMed PMID: 20561106.
60. Segawa M, Fukuda K, Nakano M, Kondo M, Satake H, Hirano M, et al. Time Course and Factors Correlating With Ventricular Tachyarrhythmias After Introduction of Steroid Therapy in Cardiac Sarcoidosis. Circ Arrhythm Electrophysiol. 2016;9(6). doi: 10.1161/CIRCEP.115.003353. PubMed PMID: 27301264.
61. Muser D, Santangeli P, Castro SA, Liang JJ, Enriquez A, Werner TJ, et al. Prognostic role of serial quantitative evaluation of. Eur J Nucl Med Mol Imaging. 2018;45(8):1394-404. Epub 2018/04/02. doi: 10.1007/s00259-018-4001-8. PubMed PMID: 29610956.
62. Kumar S, Barbhaiya C, Nagashima K, Choi EK, Epstein LM, John RM, et al. Ventricular tachycardia in cardiac sarcoidosis: characterization of ventricular substrate and outcomes of catheter ablation. Circ Arrhythm Electrophysiol. 2015;8(1):87-93. Epub 2014/12/19. doi: 10.1161/CIRCEP.114.002145. PubMed PMID: 25527825.
63. Koplan BA, Soejima K, Baughman K, Epstein LM, Stevenson WG. Refractory ventricular tachycardia secondary to cardiac sarcoid: electrophysiologic characteristics, mapping, and ablation. Heart Rhythm. 2006;3(8):924-9. Epub 2006/03/30. doi: 10.1016/j.hrthm.2006.03.031. PubMed PMID: 16876741.
64. Griffin JM, Chasler J, Wand AL, Okada DR, Smith JN, Saad E, et al. Management of Cardiac Sarcoidosis Using Mycophenolate Mofetil as a Steroid-Sparing Agent. J Card Fail. 2021;27(12):1348-58. Epub 2021/06/25. doi: 10.1016/j.cardfail.2021.06.010. PubMed PMID: 34166800.
65. Sahoo DH, Bandyopadhyay D, Xu M, Pearson K, Parambil JG, Lazar CA, et al. Effectiveness and safety of leflunomide for pulmonary and extrapulmonary sarcoidosis. Eur Respir J. 2011;38(5):1145-50. Epub 2011/05/14. doi: 10.1183/09031936.00195010. PubMed PMID: 21565914.
66. Baughman RP, Lower EE. Leflunomide for chronic sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2004;21(1):43-8. PubMed PMID: 15127974.
67. Majithia V, Sanders S, Harisdangkul V, Wilson JG. Successful treatment of sarcoidosis with leflunomide. Rheumatology (Oxford). 2003;42(5):700-2. doi: 10.1093/rheumatology/keg156. PubMed PMID: 12709556.
68. Fussner L, Karlstedt E, Fine N, Kalra S, Carmona E, Utz J, et al. Multicenter Experience With Mycophenolate Mofetil in Cardiac Sarcoidosis. CHEST. 2016;150(4):512A. doi: http://dx.doi.org/10.1016/j.chest.2016.08.526.
69. Demeter SL. Myocardial sarcoidosis unresponsive to steroids. Treatment with cyclophosphamide. Chest. 1988;94(1):202-3. Epub 1988/07/01. doi: 10.1378/chest.94.1.202. PubMed PMID: 3383636.
70. Gallegos C, Oikonomou EK, Grimshaw A, Gulati M, Young BD, Miller EJ. Non-steroidal treatment of cardiac sarcoidosis: A systematic review. Int J Cardiol Heart Vasc. 2021;34:100782. Epub 2021/05/18. doi: 10.1016/j.ijcha.2021.100782. PubMed PMID: 33997256; PubMed Central PMCID: PMC8105294.
71. Ribeiro Neto ML, Jellis CL, Joyce E, Callahan TD, Hachamovitch R, Culver DA. Update in Cardiac Sarcoidosis. Ann Am Thorac Soc. 2019;16(11):1341-50. doi: 10.1513/AnnalsATS.201902-119CME. PubMed PMID: 31322914.
72. Nagai S, Yokomatsu T, Tanizawa K, Ikezoe K, Handa T, Ito Y, et al. Treatment with methotrexate and low-dose corticosteroids in sarcoidosis patients with cardiac lesions. Intern Med. 2014;53(23):2761. Epub 2014/12/03. doi: 10.2169/internalmedicine.53.3120. PubMed PMID: 25447669.
73. Baughman RP, Winget DB, Lower EE. Methotrexate is steroid sparing in acute sarcoidosis: results of a double blind, randomized trial. Sarcoidosis Vasc Diffuse Lung Dis. 2000;17(1):60-6. PubMed PMID: 10746262.
74. Cremers JP, Drent M, Bast A, Shigemitsu H, Baughman RP, Valeyre D, et al. Multinational evidence-based World Association of Sarcoidosis and Other Granulomatous Disorders recommendations

for the use of methotrexate in sarcoidosis: integrating systematic literature research and expert opinion of sarcoidologists worldwide. Curr Opin Pulm Med. 2013;19(5):545-61. doi: 10.1097/MCP.0b013e3283642a7a. PubMed PMID: 23880702.
75. Lower EE, Baughman RP. The use of low dose methotrexate in refractory sarcoidosis. Am J Med Sci. 1990;299(3):153-7. PubMed PMID: 2316559.
76. Gerke AK. Treatment of Sarcoidosis: A Multidisciplinary Approach. Front Immunol. 2020;11:545413. Epub 2020/12/18. doi: 10.3389/fimmu.2020.545413. PubMed PMID: 33329511; PubMed Central PMCID: PMC7732561.
77. Montesinos MC, Desai A, Delano D, Chen JF, Fink JS, Jacobson MA, et al. Adenosine A2A or A3 receptors are required for inhibition of inflammation by methotrexate and its analog MX-68. Arthritis Rheum. 2003;48(1):240-7. Epub 2003/01/16. doi: 10.1002/art.10712. PubMed PMID: 12528125.
78. Cronstein BN, Naime D, Ostad E. The antiinflammatory effects of methotrexate are mediated by adenosine. Adv Exp Med Biol. 1994;370:411-6. Epub 1994/01/01. doi: 10.1007/978-1-4615-2584-4_89. PubMed PMID: 7660940.
79. Montesinos MC, Takedachi M, Thompson LF, Wilder TF, Fernandez P, Cronstein BN. The antiinflammatory mechanism of methotrexate depends on extracellular conversion of adenine nucleotides to adenosine by ecto-5'-nucleotidase: findings in a study of ecto-5'-nucleotidase gene-deficient mice. Arthritis Rheum. 2007;56(5):1440-5. Epub 2007/05/01. doi: 10.1002/art.22643. PubMed PMID: 17469101.
80. Gerards AH, de Lathouder S, de Groot ER, Dijkmans BA, Aarden LA. Inhibition of cytokine production by methotrexate. Studies in healthy volunteers and patients with rheumatoid arthritis. Rheumatology (Oxford). 2003;42(10):1189-96. Epub 2003/06/05. doi: 10.1093/rheumatology/keg323. PubMed PMID: 12777636.
81. Baughman RP, Cremers JP, Harmon M, Lower EE, Drent M. Methotrexate in sarcoidosis: hematologic and hepatic toxicity encountered in a large cohort over a six year period. Sarcoidosis Vasc Diffuse Lung Dis. 2020;37(3):e2020001. Epub 2020/12/03. doi: 10.36141/svdld.v37i3.9362. PubMed PMID: 33264378; PubMed Central PMCID: PMC7690061.
82. Vorselaars AD, Cremers JP, Grutters JC, Drent M. Cytotoxic agents in sarcoidosis: which one should we choose? Curr Opin Pulm Med. 2014;20(5):479-87. Epub 2014/07/22. doi: 10.1097/MCP.0000000000000078. PubMed PMID: 25046427.
83. Lewis SJ, Ainslie GM, Bateman ED. Efficacy of azathioprine as second-line treatment in pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 1999;16(1):87-92. PubMed PMID: 10207946.
84. Muller-Quernheim J, Kienast K, Held M, Pfeifer S, Costabel U. Treatment of chronic sarcoidosis with an azathioprine/prednisolone regimen. Eur Respir J. 1999;14(5):1117-22. PubMed PMID: 10596700.
85. Vorselaars ADM, Wuyts WA, Vorselaars VMM, Zanen P, Deneer VHM, Veltkamp M, et al. Methotrexate vs azathioprine in second-line therapy of sarcoidosis. Chest. 2013;144(3):805-12. doi: 10.1378/chest.12-1728. PubMed PMID: 23538719.
86. Rossides M, Kullberg S, Di Giuseppe D, Eklund A, Grunewald J, Askling J, et al. Infection risk in sarcoidosis patients treated with methotrexate compared to azathioprine: A retrospective 'target trial' emulated with Swedish real-world data. Respirology. 2021;26(5):452-60. Epub 2021/01/06. doi: 10.1111/resp.14001. PubMed PMID: 33398914.
87. Trivieri MG, Spagnolo P, Birnie D, Liu P, Drake W, Kovacic JC, et al. Challenges in Cardiac and Pulmonary Sarcoidosis: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;76(16):1878-901. Epub 2020/10/17. doi: 10.1016/j.jacc.2020.08.042. PubMed PMID: 33059834; PubMed Central PMCID: PMC7808240.
88. Pavelcova K, Hanova P, Ciferska H, Hasikova L, Stiburkova B. The Examination of a TPMT Gene Before Administration of Azathioprine in Rheumatology Practice and Identification of a Novel Variant p.W29R. J Clin Rheumatol. 2021. Epub 2021/12/07. doi: 10.1097/RHU.0000000000001727. PubMed PMID: 34870401.
89. Jiyad Z, Olsen CM, Burke MT, Isbel NM, Green AC. Azathioprine and Risk of Skin Cancer in Organ Transplant Recipients: Systematic Review and Meta-Analysis. Am J Transplant. 2016;16(12):3490-503. Epub 2016/05/11. doi: 10.1111/ajt.13863. PubMed PMID: 27163483.
90. Pasternak B, Svanstrom H, Schmiegelow K, Jess T, Hviid A. Use of azathioprine and the risk of cancer in inflammatory bowel disease. Am J Epidemiol. 2013;177(11):1296-305. Epub 2013/03/22. doi: 10.1093/aje/kws375. PubMed PMID: 23514635.
91. Silman AJ, Petrie J, Hazleman B, Evans SJ. Lymphoproliferative cancer and other malignancy in patients with rheumatoid arthritis treated with azathioprine: a 20 year follow up study. Ann Rheum Dis. 1988;47(12):988-92. Epub 1988/12/01. doi: 10.1136/ard.47.12.988. PubMed PMID: 3207388; PubMed Central PMCID: PMC1003651.
92. Zhang Z, Wang M, Xu L, Jiang B, Jin T, Shi T, et al. Cancer occurrence following azathioprine treatment in myasthenia gravis patients: A systematic review and meta-analysis. J Clin Neurosci. 2021;88:70-4. Epub 2021/05/17. doi: 10.1016/j.jocn.2021.03.015. PubMed PMID: 33992207.
93. Allison AC. Mechanisms of action of mycophenolate mofetil. Lupus. 2005;14 Suppl 1:s2-8. Epub 2005/04/05. doi: 10.1191/0961203305lu2109oa. PubMed PMID: 15803924.
94. Yashima Y, Ohgane T. [Pharmacological profiles of mycophenolate mofetil (CellCept), a new immunosuppressive agent]. Nihon Yakurigaku Zasshi. 2001;117(2):131-7. Epub 2001/03/10. doi: 10.1254/fpj.117.131. PubMed PMID: 11233304.
95. Allison AC, Eugui EM. Mycophenolate mofetil and its mechanisms of action. Immunopharmacology. 2000;47(2-3):85-118. Epub 2000/07/06. doi: 10.1016/s0162-3109(00)00188-0. PubMed PMID: 10878285.
96. Godziszewska S, Widuchowska M, Kope -M drek M, Kucharz EJ. Coexistence of systemic sclerosis and sarcoidosis. Wiad Lek. 2016;69(4):693-4. PubMed PMID: 27941212.
97. Kikuchi N, Nunoda S, Serizawa N, Suzuki A, Suzuki T, Fukushima K, et al. Combination therapy with corticosteroid and mycophenolate mofetil in a case of refractory cardiac sarcoidosis. J Cardiol Cases. 2016;13(4):125-8. Epub 2016/03/06. doi: 10.1016/j.jccase.2015.12.008. PubMed PMID: 30546624; PubMed Central PMCID: PMC6280734.
98. Hamzeh N, Voelker A, Forssén A, Gottschall EB, Rose C, Mroz P, et al. Efficacy of mycophenolate mofetil in sarcoidosis. Respir Med. 2014;108(11):1663-9. Epub 2014/09/28. doi: 10.1016/j.rmed.2014.09.013. PubMed PMID: 25301291; PubMed Central PMCID: PMC4254196.
99. Allison AC, Eugui EM. Mechanisms of action of mycophenolate mofetil in preventing acute and chronic allograft rejection. Transplantation. 2005;80(2 Suppl):S181-90. Epub 2005/10/28. doi: 10.1097/01.tp.0000186390.10150.66. PubMed PMID: 16251851.
100. Fox RI, Herrmann ML, Frangou CG, Wahl GM, Morris RE, Strand V, et al. Mechanism of action for leflunomide in rheumatoid arthritis. Clin Immunol. 1999;93(3):198-208. Epub 1999/12/22. doi: 10.1006/clim.1999.4777. PubMed PMID: 10600330.
101. Herrmann ML, Schleyerbach R, Kirschbaum BJ. Leflunomide: an immunomodulatory drug for the treatment of rheumatoid arthritis and other autoimmune diseases. Immunopharmacology. 2000;47(2-3):273-89. Epub 2000/07/06. doi: 10.1016/s0162-3109(00)00191-0. PubMed PMID: 10878294.
102. Breedveld FC, Dayer JM. Leflunomide: mode of action in the treatment of rheumatoid arthritis. Ann Rheum Dis. 2000;59(11):841-9. Epub 2000/10/29. doi: 10.1136/ard.59.11.841. PubMed PMID: 11053058; PubMed Central PMCID: PMC1753034.
103. Alvarez PA, Saad AK, Flagel S, Mazzocchi O, Blanco MV. Leflunomide-induced pulmonary hypertension in a young woman with rheumatoid arthritis: a case report. Cardiovasc Toxicol.

2012;12(2):180-3. Epub 2012/01/25. doi: 10.1007/s12012-012-9153-3. PubMed PMID: 22270725.
104. Coirier V, Lescoat A, Chabanne C, Fournet M, Coiffier G, Jouneau S, et al. Pulmonary arterial hypertension in four patients treated by leflunomide. Joint Bone Spine. 2018;85(6):761-3. Epub 2018/01/14. doi: 10.1016/j.jbspin.2017.12.014. PubMed PMID: 29329993.
105. Palasset TL, Chaumais MC, Weatherald J, Savale L, Jais X, Price LC, et al. Association between Leflunomide and Pulmonary Hypertension. Ann Am Thorac Soc. 2021;18(8):1306-15. Epub 2021/01/28. doi: 10.1513/AnnalsATS.202008-913OC. PubMed PMID: 33502958.
106. Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Leflunomide Use and Risk of Lung Disease in Rheumatoid Arthritis: A Systematic Literature Review and Metaanalysis of Randomized Controlled Trials. J Rheumatol. 2016;43(5):855-60. Epub 2016/03/17. doi: 10.3899/jrheum.150674. PubMed PMID: 26980577.
107. Ogino MH, Tadi P. Cyclophosphamide. StatPearls. Treasure Island (FL)2022.
108. Kato Y, Morimoto S, Uemura A, Hiramitsu S, Ito T, Hishida H. Efficacy of corticosteroids in sarcoidosis presenting with atrioventricular block. Sarcoidosis Vasc Diffuse Lung Dis. 2003;20(2):133-7. Epub 2003/07/23. PubMed PMID: 12870723.
109. Chiba T, Nakano M, Hasebe Y, Kimura Y, Fukasawa K, Miki K, et al. Prognosis and risk stratification in cardiac sarcoidosis patients with preserved left ventricular ejection fraction. J Cardiol. 2020;75(1):34-41. Epub 2019/07/02. doi: 10.1016/j.jjcc.2019.04.016. PubMed PMID: 31277963.
110. Khan NA, Donatelli CV, Tonelli AR, Wiesen J, Ribeiro Neto ML, Sahoo D, et al. Toxicity risk from glucocorticoids in sarcoidosis patients. Respir Med. 2017;132:9-14. Epub 2017/09/08. doi: 10.1016/j.rmed.2017.09.003. PubMed PMID: 29229111.
111. Cox CE, Donohue JF, Brown CD, Kataria YP, Judson MA. Health-related quality of life of persons with sarcoidosis. Chest. 2004;125(3):997-1004. doi: 10.1378/chest.125.3.997. PubMed PMID: 15006960.
112. Judson MA, Chaudhry H, Louis A, Lee K, Yucel R. The effect of corticosteroids on quality of life in a sarcoidosis clinic: the results of a propensity analysis. Respir Med. 2015;109(4):526-31. Epub 2015/02/07. doi: 10.1016/j.rmed.2015.01.019. PubMed PMID: 25698652; PubMed Central PMCID: PMC4447298.
113. Hiramitsu S, Morimoto S, Uemura A, Kato Y, Kimura K, Ohtsuki M, et al. National survey on status of steroid therapy for cardiac sarcoidosis in Japan. Sarcoidosis Vasc Diffuse Lung Dis. 2005;22(3):210-3. Epub 2005/12/01. PubMed PMID: 16315784.
114. Okabe T, Yakushiji T, Hiroe M, Oyama Y, Igawa W, Ono M, et al. Steroid pulse therapy was effective for cardiac sarcoidosis with ventricular tachycardia and systolic dysfunction. ESC Heart Fail. 2016;3(4):288-92. doi: 10.1002/ehf2.12095. PubMed PMID: 27867531; PubMed Central PMCID: PMC5107975.
115. Slivnick JA, Betz J, Kalbfleisch S, Crouser ED, Kahwash R. High-dose intravenous glucocorticoids are effective in the acute management of ventricular arrhythmias in cardiac sarcoidosis: A case series. HeartRhythm Case Rep. 2020;6(10):706-10. Epub 2020/10/27. doi: 10.1016/j.hrcr.2020.06.028. PubMed PMID: 33101937; PubMed Central PMCID: PMC7573385.
116. Watanabe H, Eguchi K, Saitou T, Shimpo M, Hiroe M, Kario K. Cardiac sarcoidosis, the complete atrioventricular block of which was completely recovered by intravenous steroid pulse therapy. J Cardiol Cases. 2016;13(1):21-4. Epub 2015/10/20. doi: 10.1016/j.jccase.2015.09.003. PubMed PMID: 30546603; PubMed Central PMCID: PMC6281864.
117. Badsha H, Edwards CJ. Intravenous pulses of methylprednisolone for systemic lupus erythematosus. Semin Arthritis Rheum. 2003;32(6):370-7. Epub 2003/07/02. doi: 10.1053/sarh.2002.50003. PubMed PMID: 12833245.
118. Badsha H, Kong KO, Lian TY, Chan SP, Edwards CJ, Chng HH. Low-dose pulse methylprednisolone for systemic lupus erythematosus flares is efficacious and has a decreased risk of infectious complications. Lupus. 2002;11(8):508-13. Epub 2002/09/11. doi: 10.1191/0961203302lu243oa. PubMed PMID: 12220105.
119. Kong KO, Badsha H, Lian TY, Edwards CJ, Chng HH. Low-dose pulse methylprednisolone is an effective therapy for severe SLE flares. Lupus. 2004;13(3):212-3. Epub 2004/05/04. doi: 10.1191/0961203304lu510xx. PubMed PMID: 15119552.
120. Kafil TS, Sparrow R, Khan HR, Manian U, Elrayes M, Bagur R, et al. Intravenous Methylprednisolone for Ventricular Tachycardia Electrical Storm in Cardiac Sarcoidosis: Case Series and 1-Year Follow-up. JACC Clin Electrophysiol. 2021;7(4):536-7. Epub 2021/04/24. doi: 10.1016/j.jacep.2020.12.003. PubMed PMID: 33888271.
121. Jamilloux Y, Cohen-Aubart F, Chapelon-Abric C, Maucort-Boulch D, Marquet A, Pérard L, et al. Efficacy and safety of tumor necrosis factor antagonists in refractory sarcoidosis: A multicenter study of 132 patients. Semin Arthritis Rheum. 2017;47(2):288-94. Epub 2017/03/08. doi: 10.1016/j.semarthrit.2017.03.005. PubMed PMID: 28392046.
122. Krishnan M, Cupps TR, Sheikh FH. Tumor necrosis factor-alpha inhibitor use for treatment of refractory cardiac sarcoidosis in a patient with left ventricular assist device: Adalimumab use in refractory sarcoidosis in a patient with left ventricular assist device. J Heart Lung Transplant. 2020;39(12):1504-5. Epub 2020/08/25. doi: 10.1016/j.healun.2020.08.001. PubMed PMID: 32830024.
123. Miller CT, Sweiss NJ, Lu Y. FDG PET/CT Evidence of Effective Treatment of Cardiac Sarcoidosis With Adalimumab. Clin Nucl Med. 2016;41(5):417-8. Epub 2016/02/02. doi: 10.1097/RLU.0000000000001124. PubMed PMID: 26828145.
124. Rosenthal DG, Parwani P, Murray TO, Petek BJ, Benn BS, De Marco T, et al. Long-Term Corticosteroid-Sparing Immunosuppression for Cardiac Sarcoidosis. J Am Heart Assoc. 2019;8(18):e010952. Epub 2019/09/06. doi: 10.1161/JAHA.118.010952. PubMed PMID: 31538835; PubMed Central PMCID: PMC6818011.
125. Stievenart J, Le Guenno G, Ruivard M, Rieu V, Andre M, Grobost V. Case Report: TNFalpha Antagonists Are an Effective Therapy in Cardiac Sarcoidosis. Front Cardiovasc Med. 2021;8:676407. Epub 2021/06/29. doi: 10.3389/fcvm.2021.676407. PubMed PMID: 34179141; PubMed Central PMCID: PMC8226185.
126. Chung ES, Packer M, Lo KH, Fasanmade AA, Willerson JT, Anti TNFTACHFI. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-alpha, in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. Circulation. 2003;107(25):3133-40. Epub 2003/06/11. doi: 10.1161/01.CIR.0000077913.60364.D2. PubMed PMID: 12796126.
127. Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation. 2004;109(13):1594-602. Epub 2004/03/15. doi: 10.1161/01.CIR.0000124490.27666.B2. PubMed PMID: 15023878.
128. Obi ON, Lower EE, Baughman RP. Biologic and advanced immunomodulating therapeutic options for sarcoidosis: a clinical update. Expert Rev Clin Pharmacol. 2021:1-32. Epub 2021/01/26. doi: 10.1080/17512433.2021.1878024. PubMed PMID: 33487042.
129. Scallon B, Cai A, Solowski N, Rosenberg A, Song XY, Shealy D, et al. Binding and functional comparisons of two types of tumor necrosis factor antagonists. J Pharmacol Exp Ther. 2002;301(2):418-26. Epub 2002/04/19. doi: 10.1124/jpet.301.2.418. PubMed PMID: 11961039.
130. Broos CE, van Nimwegen M, Hoogsteden HC, Hendriks RW, Kool M, van den Blink B. Granuloma formation in pulmonary

sarcoidosis. Front Immunol. 2013;4:437. Epub 2013/12/10. doi: 10.3389/fimmu.2013.00437. PubMed PMID: 24339826; PubMed Central PMCID: PMC3857538.
131. Chapelon-Abric C, Saadoun D, Biard L, Sene D, Resche-Rigon M, Hervier B, et al. Long-term outcome of infliximab in severe chronic and refractory systemic sarcoidosis: a report of 16 cases. Clin Exp Rheumatol. 2015;33(4):509-15. Epub 2015/06/29. PubMed PMID: 26120779.
132. Asawaeer M, Widener B, Singhal V, DeVries MJ, Romberger DJ, Erickson AR, et al. Infliximab Treatment of Refractory Cardiac Sarcoidosis. JACC Case Rep. 2020;2(10):1553-7. Epub 2021/07/29. doi: 10.1016/j.jaccas.2020.06.041. PubMed PMID: 34317016; PubMed Central PMCID: PMC8302154.
133. Barnabe C, McMeekin J, Howarth A, Martin L. Successful treatment of cardiac sarcoidosis with infliximab. J Rheumatol. 2008;35(8):1686-7. Epub 2008/08/02. PubMed PMID: 18671332.
134. Baughman RP, Lower EE. Therapy for extrapulmonary sarcoidosis. Semin Respir Crit Care Med. 2002;23(6):589-96. doi: 10.1055/s-2002-36522. PubMed PMID: 16088654.
135. Uthman I, Touma Z, Khoury M. Cardiac sarcoidosis responding to monotherapy with infliximab. Clin Rheumatol. 2007;26(11):2001-3. Epub 2007/03/31. doi: 10.1007/s10067-007-0614-1. PubMed PMID: 17394036.
136. Judson MA, Baughman RP, Costabel U, Flavin S, Lo KH, Kavuru MS, et al. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. Eur Respir J. 2008;31(6):1189-96. Epub 2008/02/06. doi: 10.1183/09031936.00051907. PubMed PMID: 18256069.
137. Crouser ED, Lozanski G, Fox CC, Hauswirth DW, Raveendran R, Julian MW. The CD4+ lymphopenic sarcoidosis phenotype is highly responsive to anti-tumor necrosis factor-{alpha} therapy. Chest. 2010;137(6):1432-5. doi: 10.1378/chest.09-2576. PubMed PMID: 20525654.
138. Jounieaux F, Chapelon C, Valeyre D, Israel Biet D, Cottin V, Tazi A, et al. [Infliximab treatment for chronic sarcoidosis--a case series]. Rev Mal Respir. 2010;27(7):685-92. Epub 2010/07/31. doi: 10.1016/j.rmr.2010.06.011. PubMed PMID: 20863968.
139. Maneiro JR, Salgado E, Gomez-Reino JJ, Carmona L, Group BS. Efficacy and safety of TNF antagonists in sarcoidosis: data from the Spanish registry of biologics BIOBADASER and a systematic review. Semin Arthritis Rheum. 2012;42(1):89-103. Epub 2012/03/02. doi: 10.1016/j.semarthrit.2011.12.006. PubMed PMID: 22387045.
140. Drent M, Cremers JP, Jansen TL, Baughman RP. Practical eminence and experience-based recommendations for use of TNF-alpha inhibitors in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2014;31(2):91-107. PubMed PMID: 25078637.
141. Syed H, Ascoli C, Linssen CF, Vagts C, Iden T, Syed A, et al. Infection prevention in sarcoidosis: proposal for vaccination and prophylactic therapy. Sarcoidosis Vasc Diffuse Lung Dis. 2020;37(2):87-98. Epub 2020/10/24. doi: 10.36141/svdld.v37i2.9599. PubMed PMID: 33093774; PubMed Central PMCID: PMC7569559.
142. Wijnen PA, Cremers JP, Nelemans PJ, Erckens RJ, Hoitsma E, Jansen TL, et al. Association of the TNF-alpha G-308A polymorphism with TNF-inhibitor response in sarcoidosis. Eur Respir J. 2014;43(6):1730-9. Epub 2014/02/22. doi: 10.1183/09031936.00169413. PubMed PMID: 24558177.
143. Judson MA, Baughman RP, Costabel U, Mack M, Barnathan ES. The potential additional benefit of infliximab in patients with chronic pulmonary sarcoidosis already receiving corticosteroids: a retrospective analysis from a randomized clinical trial. Respir Med. 2014;108(1):189-94. Epub 2013/12/10. doi: 10.1016/j.rmed.2013.11.019. PubMed PMID: 24361164.
144. Jounieaux F, Chapelon C, Valeyre D, Israel Biet D, Cottin V, Tazi A, et al. [Infliximab treatment for chronic sarcoidosis--a case series]. Rev Mal Respir. 2010;27(7):685-92. Epub 2010/09/25. doi: 10.1016/j.rmr.2010.06.011. PubMed PMID: 20863968.
145. Lower EE, Sturdivant M, Grate L, Baughman RP. Use of third-line therapies in advanced sarcoidosis. Clin Exp Rheumatol. 2019. Epub 2019/11/20. PubMed PMID: 31820728.
146. Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Ann Intern Med. 2007;146(12):829-38. Epub 2007/05/02. doi: 10.7326/0003-4819-146-12-200706190-00159. PubMed PMID: 17470824.
147. Sandborn WJ, Hanauer S, Loftus EV, Jr., Tremaine WJ, Kane S, Cohen R, et al. An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn's disease. Am J Gastroenterol. 2004;99(10):1984-9. Epub 2004/09/28. doi: 10.1111/j.1572-0241.2004.40462.x. PubMed PMID: 15447761.
148. Crommelin HA, van der Burg LM, Vorselaars AD, Drent M, van Moorsel CH, Rijkers GT, et al. Efficacy of adalimumab in sarcoidosis patients who developed intolerance to infliximab. Respir Med. 2016;115:72-7. Epub 2016/04/23. doi: 10.1016/j.rmed.2016.04.011. PubMed PMID: 27215507.
149. Baughman RP, Lower EE, Drent M. Inhibitors of tumor necrosis factor (TNF) in sarcoidosis: who, what, and how to use them. Sarcoidosis Vasc Diffuse Lung Dis. 2008;25(2):76-89. PubMed PMID: 19382527.
150. Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, et al. Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. Ann Rheum Dis. 2007;66(7):921-6. Epub 2007/02/16. doi: 10.1136/ard.2006.065615. PubMed PMID: 17301106; PubMed Central PMCID: PMC1955110.
151. Plosker GL, Figgitt DP. Rituximab: a review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia. Drugs. 2003;63(8):803-43. Epub 2003/03/29. doi: 10.2165/00003495-200363080-00005. PubMed PMID: 12662126.
152. Cerny T, Borisch B, Introna M, Johnson P, Rose AL. Mechanism of action of rituximab. Anticancer Drugs. 2002;13 Suppl 2:S3-10. Epub 2003/04/25. doi: 10.1097/00001813-200211002-00002. PubMed PMID: 12710585.
153. Krause ML, Cooper LT, Chareonthaitawee P, Amin S. Successful use of rituximab in refractory cardiac sarcoidosis. Rheumatology (Oxford). 2016;55(1):189-91. Epub 2015/09/16. doi: 10.1093/rheumatology/kev309. PubMed PMID: 26370399.
154. Elwazir M, Krause ML, Bois JP, Christopoulos G, Kendi AT, Cooper JLT, et al. Rituximab for the Treatment of Refractory Cardiac Sarcoidosis: A Single-Center Experience. J Card Fail. 2022;28(2):247-58. Epub 2021/07/29. doi: 10.1016/j.cardfail.2021.07.008. PubMed PMID: 34320381.
155. Lower EE, Sturdivant M, Grate L, Baughman RP. Use of third-line therapies in advanced sarcoidosis. Clin Exp Rheumatol. 2020;38(5):834-40. Epub 2019/12/11. PubMed PMID: 31820728.
156. Nagai T, Nagano N, Sugano Y, Asaumi Y, Aiba T, Kanzaki H, et al. Effect of Discontinuation of Prednisolone Therapy on Risk of Cardiac Mortality Associated With Worsening Left Ventricular Dysfunction in Cardiac Sarcoidosis. Am J Cardiol. 2016;117(6):966-71. Epub 2015/12/31. doi: 10.1016/j.amjcard.2015.12.033. PubMed PMID: 26805658.