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REVIEW ARTICLE
Rare diseases of the heart

Cardiac sarcoidosis – management and prognosis (RCD code: III-3A.3)

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Abstract

Sarcoidosis is a systemic, granulomatous disease of unknown etiology. Cardiac involvement in the course of sarcoidosis occurs in 5% of patients. However, about 25% of patient with systemic/pulmonary sarcoidosis might present with asymptomatic myocardial injury. The main manifestations of cardiac sarcoidosis are conduction abnormalities, ventricular arrhythmias and heart failure. Diagnosis of cardiac sarcoidosis remains a challenge for physicians. Treatment should be introduced at the time of diagnosis to prevent potentially lethal progression of cardiac disease. Steroids are the first drugs of choice. Additional anti-sarcoidosis agents are used as alternatives or to reduce the steroids dose. Some patients require implantation of a cardioverter-defibrillator for the prevention of sudden cardiac death. Patients with refractory ventricular tachyarrhythmia or severe, intractable heart failure unresponsive to optimal pharmacotherapy, require heart transplantation. Prognosis in cardiac sarcoidosis is highly variable, dependent on location and severity of heart involvement. This article reviews current diagnostic and therapeutic recommendations for cardiac sarcoidosis. JRCD 2017; 3 (2): 37–43

Key words: rare disease, heart failure, arrhythmia, pacemaker, echocardiography

Background

Sarcoidosis is a multisystem inflammatory disease characterized by the presence of noncaseating granulomas. Most commonly lesions affect lungs, hilar lymph nodes, joints and skin. Sarcoid granulomas can localize in any other organ like heart, nervous system, eyes, liver, spleen, salivary glands, muscles and bones [1].

Heart involvement in the course of sarcoidosis can result in conduction abnormalities, arrhythmias or heart failure. Symptoms reported by patients with cardiac sarcoidosis (CS) include palpitations, chest pain, dyspnoea, syncope and peripheral edema [2]. However, in many cases, the disease remains asymptomatic [3,4].

Clinical course of CS is unpredictable, varies from asymptomatic to life-threatening events due to ventricular arrhythmias or bradycardia. Sudden cardiac death may be the first presentation of sarcoidosis.

Due to the risk of potentially life-threatening complications, all patients diagnosed with sarcoidosis should undergo screening for heart involvement [4].

Epidemiology

Cardiac involvement in the course of sarcoidosis occurs in 5% of patients [2,5,6]. However, autopsy studies suggest that the prevalence of CS is much higher, ranging up to 25% [7]. In addition, imaging studies have found heart involvement in 3,7%–54,9% of patients with extra-cardiac sarcoidosis [6]. CS may be the first manifestation of sarcoidosis [8]. Several cases of isolated CS have also been reported [8–10].

Diagnostic criteria

Latest criteria for diagnosis of CS were proposed by Heart Rhythm Society (HRS) Expert Consensus Statement on Arrhythmias Associated with Cardiac Sarcoidosis in 2014. CS should be diagnosed in the presence of non-caseating granuloma on histological examination in a sample obtained from endomyocardial biopsy [6]. However, due to low sensitivity of endomyocardial biopsy

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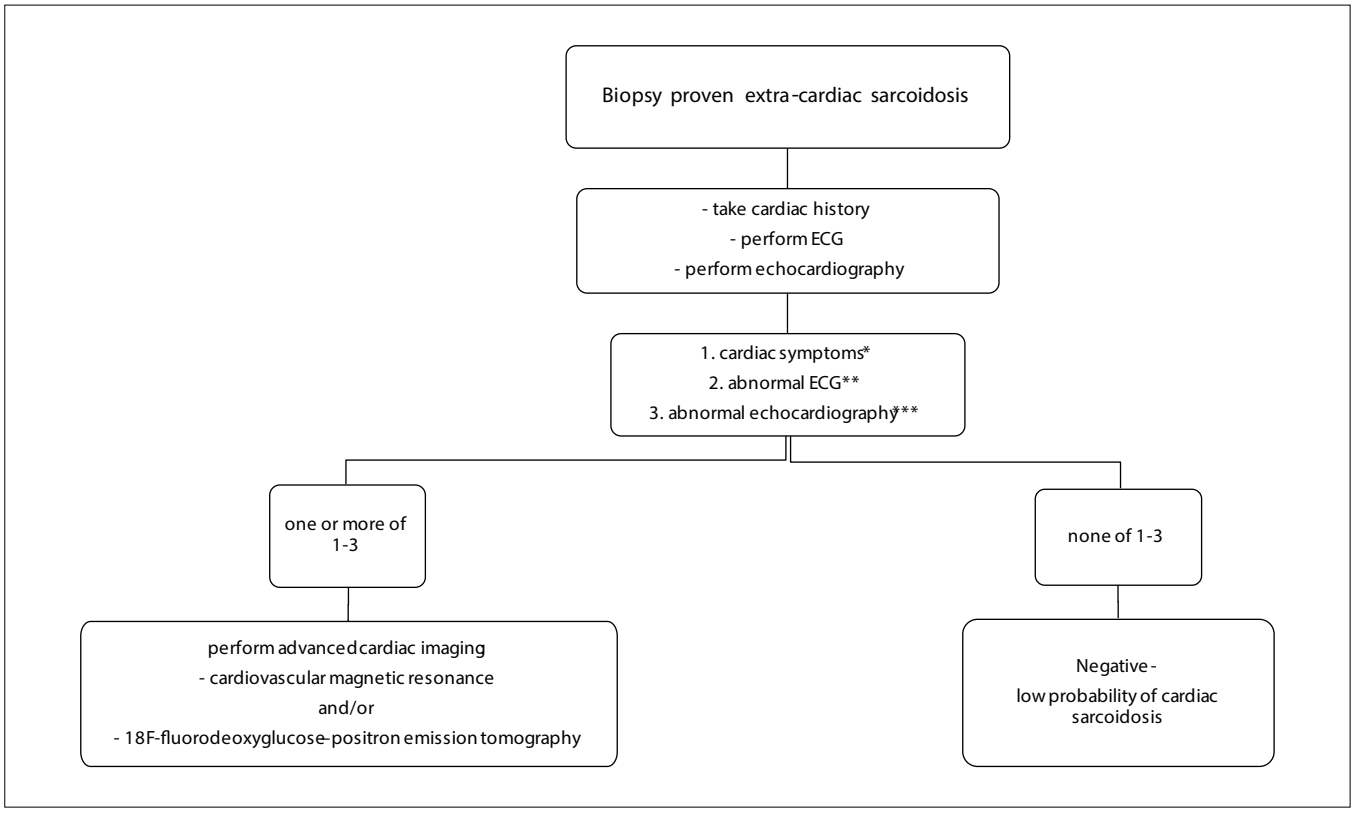

Figure 1. Diagnostic algorithm for cardiac involvement in patients with biopsy-proven extra-cardiac sarcoidosis based on Heart Rhythm Society Expert Consensus [6].* Cardiac symptoms defined as: pre-syncope, syncope, prominent palpitations lasting >2 weeks. ** Abnormal ECG defined as complete left or right bundle branch block and/or presence of unexplained pathological Q waves in 2 or more leads and/or sustained 2 or 3 degree atrioventricular block and/or sustained or non-sustained ventricular tachycardia. *** Abnormal echocardiogram defined as regional wall motion abnormality and/or wall aneurysm and/or basal septum thinning and/or left ventricular ejection fraction <40%

in the diagnosis of CS (20–30%), experts proposed other diagnostic pathways, based on a number of clinical and diagnostic criteria [11]. According to this, CS is probable in patients with biopsy proven extra-cardiac sarcoidosis if one or more of the following criteria is present:

- Steroid and/or immunosuppressant responsive cardiomyopathy or heart block
- Unexplained reduction of left ventricular ejection fraction (<40%)
- Unexplained sustained (spontaneous or induced) ventricular tachycardia
- Type 2 second-degree atrioventricular (AV) block (Mobitz II) or third-degree atrioventricular block
- Patchy uptake on cardiac positron emission tomography (PET)
- Late Gadolinium enhancement on cardiac magnetic resonance (CMR)
- Positive gallium uptake on myocardial scintigraphy
- Other causes of these changes have been excluded [6].

Screening for cardiac involvement in patients with biopsy-proven extra-cardiac sarcoidosis

Algorithm for the investigation of patients with biopsy-proven extra-cardiac sarcoidosis proposed by HRS experts is shown in Figure 1.

Management

Treatment of CS should be introduced at the time of diagnosis [12]. The main goal is to reduce the area of active inflammation and prevent transformation of sarcoid granulomas to fibrosis. These reduce the risk of sudden cardiac death and protect from deterioration of the cardiac function [2,13]. Medications used to treat CS are presented in Table 1.

Steroids

Steroids are the drugs of choice for the treatment of CS. But many issues regarding the treatment remain unclear. Problematic matters are: initiation of treatment, dose schedules, duration of treatment, long-term benefit, steroid-sparing alternatives or combination therapy [2].

Most sarcoidosis experts in the United States recommended an initiating dose of prednisolone 0.5 mg/kg/day, up to 40 mg/day orally. The majority of experts use the same dosing schedule regardless of the indication to start therapy (arrhythmia or cardiomyopathy) [14]. This initial dose should be maintained for a minimum of 6 months and then reduced to a baseline dose of 10–15 mg per day. The maintenance dose should be continued for the following 12 months [2]. Some authors suggest a higher initial dose of prednisolone of 60–80 mg per

Table 1. Drugs for the treatment of cardiac sarcoidosis [21–23,25–27]

medication name	dosage	side effects
first-line treatment		
Corticosteroids	– initial dose: 0.5 mg/kg/day for 6 months – maintenance dose: 10–15 mg/day for the following 12 months	life-threatening infections, hypertension, new-onset diabetes mellitus, Cushing syndrome, steroid myopathy, osteoporosis, peptic ulcer disease, weight gain, cataract, glaucoma wound healing impaired, bruising, insomnia, psychosis
second-line treatment		
Methotrexate	10–25 mg per week (orally or intramuscularly)	nausea, malaise, leucopenia, hepatotoxicity, pulmonary toxicity, opportunistic infections, teratogenic risks
Azathioprine	– initial dose: 50 mg/day – target dose of 2 mg/kg/day (orally)	infections, gastrointestinal complaints, hepatotoxicity hepatic function decline and bone marrow depression
Leflunomide	– initial dose: 20 mg/day (orally) – dosage may be decreased to 10 mg/day in patients who develop toxicity	nausea, diarrhea, abdominal pain, rash, alopecia, peripheral neuropathy, anemia, hepatotoxicity, teratogenic risks
Cyclophosphamide	– 500–1000 mg administered intravenously over 30–60 minutes; every 3–4 weeks	toxicity of the hematologic, dermatologic, metabolic, gastrointestinal, and genitourinary systems, infertility, carcinogenic and teratogenic risks
third-line treatment		
Infliximab	– 3–5 mg/kg intravenously at weeks 0, 2, 6, and 12	allergic reactions, leukopenia and immunosuppression, neurologic complications (e.g demyelination syndromes)
Adalimumab	– 40 mg subcutaneous injection every 1–2 weeks	infections, neutropenia, lupus-like reaction, headache, nausea, pyrosis, rash, arthritis, edema, weight loss

day and recommend the extension of therapy to 24 months [15,16]. However, the study performed in Japan concluded that there was no significant difference in the prognosis in patients treated with a high initial dose (>30 mg) as compared to a low initial dose (≤30 mg) of prednisone [17]. Early use of corticosteroids can allow recovery of AV block and improve left ventricular ejection fraction [18,19]. Steroids are less effective against ventricular arrhythmias, which most commonly are related to scar formation [20].

Main side effects are life-threatening infections, hypertension, new-onset diabetes mellitus, Cushing syndrome, steroid myopathy, osteoporosis, peptic ulcer disease, weight gain, cataract, glaucoma, impaired wound healing, bruising, insomnia, psychosis.

Second-line agents

In case of intolerance, significant side effects or lack of response to treatment with steroids other immunosuppressive drugs are recommended [12]. Additional anti-sarcoidosis agents can be used as alternatives to corticosteroids or in combination with steroids to reduce the steroids dose [2,15] Second-line medications used for the treatment of CS are methotrexate, azathioprine, leflunomide, and cyclophosphamide [21]. Among these drugs most commonly used is methotrexate [2].

Methotrexate

Methotrexate (MTX) is a folic acid antagonist inhibiting cellular proliferation. However, current evidence has shown that its anti-inflammatory mechanism of action is more likely the result of stimulation of adenosine release. MTX is considered to be the first-choice second-line therapeutic option in sarcoidosis [22].

The typical dose of MTX for sarcoidosis is 10–25 mg per week. This agent can be administered orally or intramuscularly. Folic acid should to be added [21–23].

The most common side effects of MTX are nausea, malaise, and leucopenia. Additional side effects include hepatotoxicity, pulmonary toxicity, opportunistic infections and teratogenic risks. Women in childbearing age must use a reliable method of contraception while treatment with methotrexate [21,22].

Azathioprine

Azathioprine (AZA) is a purine antagonist which derives its anti-inflammatory effect mainly through reducing B- and T-cell proliferation. AZA is often used in cases when MTX is contraindicated or failed to induce response. This agent is administered orally. The initial dose of AZA is 50 mg/day, the maintenance dose is 2 mg/kg/day, with a maximum of 200 mg/day. The clinical response is usually delayed by 2–4 months [21,22].

Most common side effects are infections, gastrointestinal complaints, hepatic function decline and bone marrow depression [22,23].

Leflunomide

Leflunomide (LEF) represses lymphocyte responses only in actively stimulated lymphocyte clones. The starting dose is 20 mg/day given orally. Dose 10 mg/day is indicated for patients who develop toxicity. Reported side effects include gastrointestinal symptoms, liver test abnormalities and peripheral neuropathy [21,22].

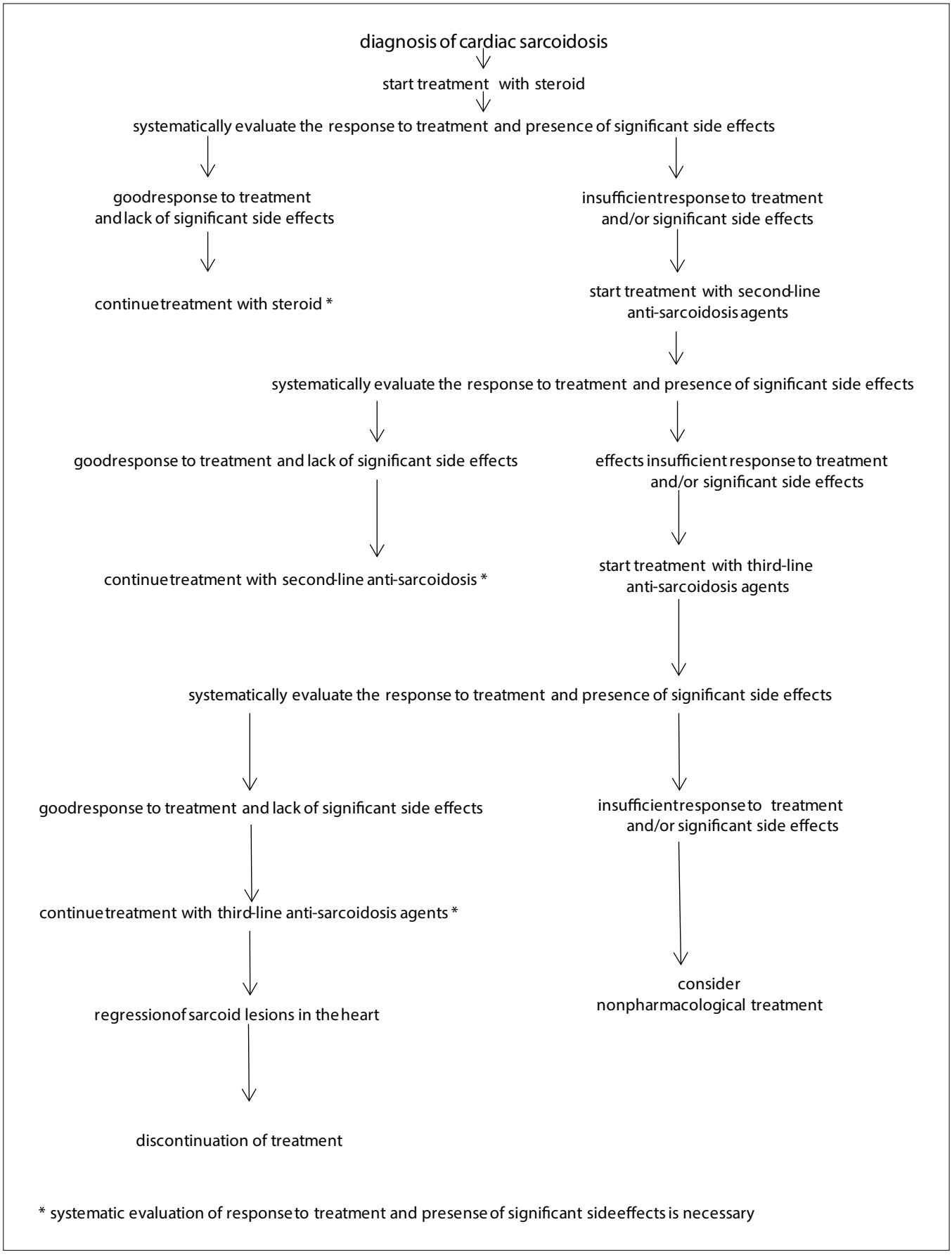

Figure 2. Treatment algorithm of cardiac sarcoidosis proposed by authors

Table 2. Recommendations for ICD implantation in patients with cardiac sarcoidosis based on Heart Rhythm Society Expert Consensus [6]

ICD is recommended – Class I	Spontaneous sustained ventricular arrhythmias, including cardiac arrest in history AND/OR The LVEF is ≤ 35% despite the use of optimal pharmacotherapy and immunosuppressive treatment (if there is active myocardial inflammation)
ICD can be useful – Class IIa	The presence of indication for permanent pacemaker implantation AND/OR History of unexplained syncope or near-syncope, likely to be arrhythmic in etiology AND/OR Inducible ventricular arrhythmias (> 30 seconds of monomorphic VT, or clinically relevant polymorphic VT/ventricular fibrillation)
ICD may be considered – Class IIb	LVEF 36–49% and/or RV ejection fraction < 40%, despite the use of optimal pharmacotherapy and immunosuppressive treatment (if there is active myocardial inflammation)
ICD not recommended – Class III	Normal left and right ventricular ejection fraction, no history of syncope or near-syncope, no indication for permanent pacemaker implantation, no late gadolinium enhancement on cardiac magnetic resonance and negative *electrophysiology study*. However, these patients should be closely followed for deterioration of the cardiac function AND/OR Incessant ventricular arrhythmias AND/OR Severe heart failure in NYHA class IV

ICD – implantable cardioverter-defibrillator, LVEF – left ventricular ejection fraction, RV – right ventricle, VT – ventricular tachycardia, NYHA – New York Heart Association

Cyclophosphamide

Cyclophosphamide (CP), a cytostatic agent, leads to inhibition of lymphocyte number and function with suppression of both cellular and humoral immunity. The dose of CP is: 500–1000 mg administered over 30–60 minutes, every 3–4 weeks, injected intravenously. Adverse events include gastrointestinal complaints, infections, bone marrow suppression and hemorrhagic cystitis [21,22].

Third-line therapy: biological agents

Tumor necrosis alpha antagonists

Tumor necrosis factor alfa (TNF-α) is thought to be involved in the development of sarcoid granulomas. Data suggest that TNF-α antagonists such as infliximab and adalimumab are effective for pulmonary and extra-pulmonary sarcoidosis [24]. All patients treated with biological agents should receive annual influenza vaccination and periodic pneumococcal vaccination. Screening for active or latent tuberculosis infection is recommended, because an increased risk of tuberculosis reactivation. To prevent the formation of antidrug antibodies, concurrent MTX or other cytotoxic drug use is advised [22].

Infliximab

Infliximab often shows a therapeutic response within a few weeks, unlike most other anti-sarcoidosis agents which are characterized by prolonged onset of action [21]. The dose of Infliximab is 3–5 mg/kg at weeks 0, 2, 6, and 12, given intravenously [23].

Infliximab increases the risk of infection. Cases of fatal cryptococcosis have been reported in patients with CS treated with infliximab [12]. Other side effects of infliximab are allergic reactions and heart failure [22].

Adalimumab

Adalimumab is a fully human anti-TNF α monoclonal antibody. Adalimumab is an effective alternative for sarcoidosis patients who become intolerant to infliximab because of an allergic reaction, antibody formation against infliximab. After switching to adalimumab 39% of patients achieved clinical improvement and 33% stabilization. The typical dose for this agent is 40 mg every 1–2 weeks, intramuscularly [22,25].

Toxicities are usually similar to infliximab. However, the risk of allergic reactions is less common, because of the fully human nature of adalimumab [22].

Proposed treatment algorithm for CS is presented in Figure 2. However, an individual approach to each patient is always necessary. Initial assessment of therapy contraindications before starting treatment is vital. Moreover, it is important to systematically evaluate both the effectiveness of therapy as well as the occurrence of any side effects. After finishing the treatment, screening for the relapse of CS is required.

Further perspectives

One of the future directions of treatment CS is personalized medicine. This term means drug selection based on analysis of patient's genotype [22]. An example is thiopurine S-methyltransferase (TPMT) genotyping before the onset of treatment with AZA. Patients with low TPMT levels have higher risk of developing myelosuppression while treatment with AZA [28]. Other example is association between polymorphisms in genes coding for TNF-α and response to treatment sarcoidosis with TNF-α inhibitors. However, further studies are necessary to evaluate the value of pharmacogenetics in the treatment of sarcoidosis [22,29].

Antiarrhythmic drugs

Ventricular arrhythmias

Amidarone and sotalol are the most widely used drugs to treat ventricular tachycardia in the course of CS [6]. Unfortunately, ventricular arrhythmias are often resistant to treatment [2]. Additionally, amiodarone can cause respiratory complications, such as pneumonitis and/or pulmonary fibrosis, which can lead to a further deterioration in respiratory function in patients with pulmonary sarcoidosis [15,30].

Atrial arrhythmias

Beta-blockers, calcium-channel blockers, sotalol, dofetilide and amiodarone are recommended for atrial arrhythmias in patient with CS. Class I antiarrhythmics agents are not recommended due to structural heart disease secondary to scarring and aneurysm formation [2,6].

Heart failure therapies

Patients with CS and heart failure should be treated according to heart failure guidelines with certain differences. Angiotensin-converting enzyme inhibitors (ACEI) are the drugs of choice for all patients with CS and impaired left ventricular systolic function. Angiotensin receptor blockers (ARB) should be administrated when ACEI are contraindicated [12,30]. Beta-blockers should be used very carefully, because they increase the risk of conduction disturbances [12,15,30]. In patients with no evidence or history of AV node dysfunction, benefits of beta-blockers would appear to outweigh the potential risk. Treatment should be initiated at low doses and increased gradually within several months [12,30]. Hydralazine and nitrate therapy can be added according to the individual indications [12]. Patient with poor left ventricular ejection fraction (LVEF ≤30%), complete left bundle branch block and advanced heart failure in New York Heart Association (NYHA) functional class III-IV despite optimal pharmacotherapy can benefit from cardiac resynchronization therapy (CRT) [31].

Device theraphy

Permanent pacemakers

Indications for permanent pacemaker implantations are similar to those in patients without CS. Permanent pacing is effective in the prevention of sudden cardiac death in advanced AV block and other bradyarrhythmias [15,30].

Implantable cardioverter-defibrillator (ICD)

The Expert Consensus writing group recommends cardioverter-defibrillator (ICD) implantation as a secondary prevention in patients with cardiac sarcoidosis and spontaneous sustained ventricular arrhythmias, including patients with history of cardiac arrest (Class I recommendation). ICD should be implanted (Class I), as a primary prevention, in patients with cardiac sarcoidosis and severe reduction of left ventricular ejection fraction (LVEF ≤35%) despite optimal pharmacotherapy and treatment with immunosuppressants, if active inflammation process is detected. ICD implantation can be useful regardless of LVEF in CS patients with: (1) indications for pacemaker implantation, (2) unexplained syncope or near-syncope, likely to be arrhythmic in etiology, and (3) inducible sustained ventricular arrhythmias (>30 seconds) or clinically relevant ventricular fibrillation (VF) (Class IIa). ICD may be considered (Class IIb) for patients with mild impairment of left ventricular systolic function (LVEF 36–49%) and/or deterioration in right ventricle function with ejection fraction less than 40% despite optimal medical therapy and a trial of immunosuppression if indicated. ICD implantation is not recommended (Class III) in patients with no history of syncope, normal left and right ventricular function, no delayed enhancement on CMR, negative electrophysiology study, and no indication for permanent pacemaker implantation. Close monitoring for worsening of ventricular function in these patients is necessary. Finally, ICD implantation is not recommended in CS patients with incessant ventricular arrhythmias and/or advanced heart failure with NYHA class IV [6,32].

Indications for ICD implantation are presented in Table 2.

Cardiac ablation therapies

A result of involvement of the basal part of right ventricle in the course of sarcoidosis may be ventricular arrhythmias. They arise in the mechanism of reentry in the peritricuspid area. Patients with CS and sustained ventricular tachycardia refractory to medical therapy may benefit from electrical ablation. Cardiac ablation may completely eliminate or reduce the frequency of ventricular tachycardia [33,34]. Data on cardiac ablation of atrial arrhythmias in CS are insufficient [6].

Heart transplantation

Heart transplantation for cardiac sarcoidosis is extremely rare. It should be considered in patient with resistant ventricular tachyarrhythmia or severe, intractable heart failure refractory to optimal pharmacotherapy, especially in younger patients [15,33]. 1-year survival rates for heart transplant recipients with cardiac sarcoidosis is similar to the general cardiac transplant population (87,7% versus 84,5%) [35]. Sarcoidosis may recur in the transplanted heart. Recurrence of the disease was documented from 24 weeks to 19 months after transplantation [15,35]. Low-doses of steroids can prevent recurrence of the disease [2]. On the other hand sarcoidosis can be transmitted to the recipient by a donor heart [36].

Prognosis

Prognosis of CS depends on the extent and location of heart involvement [33]. Overall 5-year survival rate in treated patients with preserved ventricular systolic function ranges from 60–90%. Among untreated patients 5-year survival rate is 10% [4,37]. Most deaths due to cardiac sarcoidosis are caused by arrhythmias or conduction disturbances. Progressive heart failure due to massive granulomatous infiltration of the myocardium causes 25% of

deaths [33]. Reduced LVEF is an adverse prognostic factor. Steroid-treated patients with LVEF of ≥50% had significantly greater survival rates than those with LVEF of <50% [17]. Independent predictors of mortality in steroid-treated patients with CS are NYHA class III or IV, enlarged left ventricular end-diastolic diameter, and the presence of sustained ventricular tachycardia. Early corticosteroid therapy improves prognosis if applied before the impairment of left ventricular systolic function [17].

Conclusions

Cardiac sarcoidosis is present in about 5% of patients with systemic sarcoidosis. Many patients with CS might present with asymptomatic myocardial injury. Undiagnosed, untreated disease progresses, leading to myocardial dysfunction. The most common signs of heart involvement are AV block, ventricular arrhythmias and congestive heart failure.

Pharmacotherapy of CS include corticosteroids and cytotoxic or biological agents. Early inclusion of proper therapy decrease the likelihood of developing complications. Some patients require device therapy (permanent pacemakers or ICD). Heart transplantation is an option for patients with end-stage CS resistant to medical therapy. The most important prognostic factors of mortality in steroid-treated patients is the severity of heart failure.

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