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Cardiac Sarcoidosis multi-center randomized controlled trial (CHASM CS-RCT)*

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Abstract

Background—Approximately 5% of patients with sarcoidosis have clinically manifest cardiac involvement. Clinical features of Cardiac Sarcoidosis are dependent on the location, extent, and activity of the disease. First line therapy is usually with prednisone and this is recommended based on clinician experience, expert opinion and small observational cohorts. There are no published clinical trials in cardiac sarcoidosis and multiple experts in the field have called for randomized

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Appendix. Supplementary data

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clinical trials to answer important patient care questions. Corticosteroid are associated with multiple adverse effects including hypertension, diabetes, weight gain, osteoporosis, and increased risk of infections. In contrast Methotrexate is generally well tolerated and is increasingly used in other forms of sarcoidosis.

Objectives—The Cardiac Sarcoidosis Multi-Center Randomized Controlled Trial (CHASM CS-RCT; [NCT03593759](#)) is a multicenter randomized controlled trial designed to evaluate the optimal initial treatment strategy for patients with active cardiac sarcoidosis. We hypothesize that (1) a low dose prednisone/methotrexate combination will have non-inferior efficacy to standard dose prednisone and that (2) the low dose prednisone/ methotrexate combination will result in significantly better quality of life than standard dose prednisone, as a result of reduced burden of side effects.

Methods/design—Eligible study subjects will have active clinically manifest cardiac sarcoidosis presenting with one or more of the following clinical findings: advanced conduction system disease, significant sinus node dysfunction, non-sustained or sustained ventricular arrhythmia, left ventricular dysfunction or right ventricular dysfunction. Subjects will be randomized in a 1:1 ratio to prednisone 0.5 mg/kg/day for 6 months (maximum dose 30 mg daily) OR to 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. The primary endpoint is summed perfusion rest score on 6-month PET (blinded core-lab review). The summed perfusion rest score is measure of myocardial fibrosis/scar. The design is non-inferiority with a sample size of 97 per group.

Discussion—Given the multiorgan system potential adverse side effects of prednisone, proving noninferiority of an alternate regimen would be sufficient to make the alternative compare favorably to standard dose steroids. This is the first ever clinical trial in cardiac sarcoidosis and thus in addition to the listed goals of the trial, we will also establish a multi-center, multinational cardiac sarcoidosis clinical trials network. Such a collaborative infrastructure will enable a new era of high quality data to guide physicians when treating cardiac sarcoidosis patients.

Background

Sarcoidosis is a multisystem, granulomatous disease seen worldwide, with a prevalence of about 4.7 to 64 in 100,000; reported rates are highest in individuals of northern European and African-American descent, especially women.^{1,2} The etiology of sarcoidosis is unknown, but there is growing evidence to suggest an immunological response to an unidentified antigenic trigger in individuals with genetic susceptibility.³ Approximately 5% of patients with sarcoidosis have clinically manifest cardiac involvement. Clinical features of Cardiac Sarcoidosis (CS) are dependent on the location, extent, and activity of the disease. Patients present with one or more of ventricular arrhythmias, conduction abnormalities, and heart failure. Indeed, cardiac presentations can often be the first manifestation of sarcoidosis. Studies suggest an increasing prevalence of CS; however, this is most likely the result of enhanced imaging technology and/or more in-depth investigation^{4,5} In addition, there is mounting awareness that CS can be the earliest sign of sarcoidosis.^{6–9}

Many patients with extra-cardiac sarcoidosis undergo spontaneous remission without treatment and, particularly with cardiac involvement, there is no easy way to assess disease activity or severity.¹⁰ There is also conflicting data on the efficacy of steroids on long-term disease outcomes.^{11–13} Indeed some data suggests that routine administration of systemic steroid therapy may actually increase the possibility of relapsing disease, rather than a sustained remission.¹³ The usual indication for therapy of pulmonary sarcoidosis is a combination of symptoms, deteriorating lung function and progressive radiographic change.¹⁴ Treatment of cardiac ocular, neurologic, or renal sarcoidosis or hypercalcemia is generally recommended. However, this is based on expert opinion.³ There has never been a clinical trial in cardiac sarcoidosis. A systematic review of clinical reports of corticosteroids for the treatment of CS was recently published.¹⁵ The highest quality data related to heart block; because of limitations in data quality, no clear conclusions could be established for other outcomes.¹⁵ Twenty seven of 57 patients (47%) treated with corticosteroids had improvements in conduction while in contrast, out of 16 patients not treated with corticosteroids, 0/16 improved.¹⁵ Data on LV function and response to steroids is variable¹⁵, and maybe related to reduction in inflammation.¹⁶ Supplementary Table 1 is summary of studies reporting outcomes after prednisone and/or methotrexate.

Corticosteroid are associated with multiple adverse effects including hypertension, diabetes, weight gain, osteoporosis, and increased risk of infections. The dose of corticosteroids that patients receive has an important effect on patient quality of life (QoL). For example, Judson et al.¹⁷ showed that sarcoidosis patients who received <500 mg of prednisone in the previous year had an improved health related QoL compared to patients receiving >500 mg after adjusting for severity of illness. The authors concluded “these data support the need to continue to search for effective alternative medications to corticosteroids.” In contrast Methotrexate is generally well tolerated and based on acceptable safety profile, Methotrexate is considered appropriate for long-term use.¹⁸ Methotrexate is the most widely used steroid sparing agent in sarcoidosis.¹⁸ One small open-label study, Nagai¹⁹ et al. longitudinally followed 17 CS patients who received prednisolone and methotrexate (n = 10) compared with patients who received only corticosteroids (n = 7). The study showed that EF was significantly stabilized in the combination therapy group but not in the corticosteroids alone group at three years after the first treatment. The most commonly observed side effects of Methotrexate at doses typically used for the treatment of sarcoidosis are rarely life-threatening, these include: stomatitis or soreness of the mouth, abnormal liver function tests, which are typically mild elevations in hepatic transaminases, rash, headache, fatigue, malaise, alopecia, and hematologic abnormalities, particularly macrocytosis, in addition to infrequent but severe myelosuppression.¹⁸

The Cardiac Sarcoidosis Multi-Center Randomized Controlled Trial (CHASM CS-RCT; [NCT03593759](#)) is a multicenter randomized controlled trial designed to evaluate the optimal initial treatment strategy for patients with clinically active cardiac sarcoidosis. We hypothesize that (1) low dose prednisone/methotrexate combination will have non-inferior efficacy to standard dose prednisone and that (2) the low dose prednisone/ methotrexate combination will result in significantly better quality of life than standard dose prednisone, as a result of reduced burden of side effects. Given the multiorgan system potential adverse

side effects of prednisone, proving noninferiority of an alternate regimen would be sufficient to make the alternative compare favorably to standard dose steroids.

Methods

Study design

The CHASM CS-RCT is a prospective, open-label, non-inferiority, randomized controlled trial (1:1 randomization) with blinded end-point analysis. Patients with clinically active cardiac sarcoidosis and positive FDG uptake on PET within two months will be included in the study. Eligible and consenting patients will be equally randomized to control or experimental groups. The randomization will be blocked using blocks of varying sizes. Randomization will be done electronically using web-based software (Dacima, Montreal, Canada).

Study Setting and Timeline

This is a multicenter trial involving centers with high volume cardiac sarcoidosis experience in Canada (8 centers), the United States (3 centers), Japan (9 centers) and the United Kingdom (2 centers). The protocol has been approved by Health Canada and the Food and Drug Administration (US). Enrollment began at one center in late Jan 2019 and five patients have been recruited. Ten additional US and Canadian centers will be activated between August and November 2019 and expansion to Japanese and UK sites will follow. We aim to complete enrollment in 48 months and subjects will be followed for 6 months.

Funding

Pilot funding for the vanguard phase of CHASM CS-RCT comes from the Canadian Institute for Health Research (CIHR). In addition, the trial is supported by the Virginia Commonwealth University Johnson Center for Pulmonary and Critical Care Research.

Study Population

Written informed consent will be obtained from each subject. Eligible study subjects will have active clinically manifest cardiac sarcoidosis. Inclusion and exclusion criteria are shown in Table 1.

Interventions

Subjects will be randomized in a 1:1 ratio to prednisone 0.5 mg/kg/day for 6 months (maximum dose 30 mg daily) OR to 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 orally, subcutaneously or intramuscular weekly for 6 months AND folic acid 2 mg daily for 6 months. The dose of prednisone (in both arms) and methotrexate were selected based on expert opinion and consensus of the steering committee. Also, the maximum dose of prednisone was selected to (i) reduce side effects¹⁷ (ii) and based on data that showed no significant difference in prognosis in those patients treated with greater than 40 mg of prednisone per day compared to those treated with 30 mg or less.²⁰ The study flow chart is shown in Figure 1.

Assessments

Cardiac Positron Emission Tomography (PET) will be performed at baseline and at 6 months. There are standardized operating procedures for all aspects of the PET scans including site selection, patient preparation, image acquisition, image processing, transfer to the core lab and analysis at core lab. All PET scans will include cardiac perfusion and F18-Fluorodeoxyglucose (FDG) imaging as well as whole-body FDG PET. After 6-months further management will be at treating physician's discretion. ECG and echocardiography will be performed at baseline and 6 months. Biomarkers will be evaluated at baseline and 6 months. Blood will be sent to a biomarker core-lab. Biomarkers to be assayed will include highly sensitive troponin I, brain natriuretic peptide (BNP), hs C-reactive protein (CRP). We will also store samples for future novel biomarker discovery. Potential candidates include biomarkers related to cardiac matrix turnover or fibrosis (e.g. serum detectable soluble matrix metalloproteinases).²¹

Quality of life assessments will be performed at baseline, 12 weeks, and 6 months. We will assess both generic QoL using SF 36 and disease-specific QoL using the Kings Sarcoidosis Questionnaire (KSQ)²² and the Sarcoidosis Assessment Tool (SAT).²³ Cardiac MR at baseline and 6 months will be optional but strongly encouraged. Supplementary Tables 2 and 3 are summaries of study procedures.

Primary Endpoint

The primary endpoint is summed perfusion rest score (SPRS) on 6-month FU PET scan by blinded core lab analysis. The primary endpoint was selected based on expert opinion and consensus of the steering committee. While MRI is considered the gold standard for myocardial scar/fibrosis assessment, most of the patients will have implantable cardiac devices, which is a relative contraindication to MRI scanning and can cause artifact that limits scan interpretation. The summed perfusion rest score is measure of myocardial fibrosis. As the primary aim of therapy in sarcoidosis is to prevent end organ damage due to fibrosis, the SPRS is an appropriate primary endpoint assessment. Suppression of inflammation was considered by the steering committee to be of secondary importance.

Secondary Endpoints

Secondary endpoints will include mortality, cardiovascular hospitalizations, medication adverse events, medication toxicity, generic and disease-specific QoL scores, extra-cardiac disease activity on PET, LV and RV ejection fraction on PET and echocardiogram, ventricular arrhythmia burden, biomarkers, and burden of late gadolinium enhancement. Full details of secondary endpoints are shown in Table 2.

Planned Analyses

Descriptive statistics including 95% confidence intervals will be calculated for all baseline variables using means, medians, standard deviations and interquartile ranges for continuous outcomes, and rates and proportions for discrete outcomes for each treatment arm. For the primary outcome, SPRS, the two arms will be compared using the T-test. Baseline characteristics of the treatment arms will be compared. If any clinically significant differences are identified, a logistic regression analysis will be conducted to compare the

primary endpoints between the two treatment arms adjusting for these differences. Similar analysis plan for the primary outcome will be followed for the secondary outcomes, using T Tests for continuous variables and Chi Square tests for categorical. There will be one interim analysis when 50% of patients have been completed follow-up. The p value at the interim analysis for 50% patients recruited will be 0.00153 and the p value for the final analysis will be 0.025.

Data Collection and Management

After the baseline and randomization visit, subjects will be seen in clinic at 4 weeks, 12 weeks, and 6 months. All data entry will be done electronically using web-based software (Dacima, Montreal, Canada). The University of Ottawa Heart Institute (UOHI) Clinical Trials Centre will function as the coordinating center for all aspects of this trial.

Sample Size Calculation

The design is non-inferiority. Pilot observational data in patients similar to that to be recruited in this study after treatment with 0.5 mg/kg of prednisone, found a mean SPRS 6.33 (SD = 7.09). Using one sided non-inferiority margins of 50% and assuming 5% dropouts in each arm and 2% crossovers (both directions), the sample size required is 97 per group. One sided test for alpha = 0.025.

Discussion

Cardiac sarcoidosis is a potentially life-threatening disease that can cause ventricular arrhythmias, conduction abnormalities, heart failure, and death. Current therapies, including steroids and steroid-sparing agents, have limited data on improved outcomes and unfavorable side effect profiles. Despite >50 years of use as the most common therapy for sarcoidosis, there is no proof of survival benefit from corticosteroid treatment. There are no evidence-based therapies for cardiac sarcoidosis, and recommendations are given based on expert opinions. There is therefore an urgent need for randomized controlled clinical trials in cardiac sarcoidosis. To our knowledge, this will be the first randomized controlled trial of therapy for cardiac sarcoidosis patients. We hypothesize that (1) low dose prednisone/ methotrexate combination will have non-inferior efficacy to standard dose prednisone and that (2) the low dose prednisone/ methotrexate combination will result in significantly better quality of life than standard dose prednisone, as a result of reduced burden of side effects.

While the primary endpoint is fibrosis on PET scan, the secondary endpoints for this trial will play a critical role in advancing our understanding and management of CS and generating hypotheses for future research in this field. To date, no biomarker exists to identify active cardiac sarcoidosis and follow response to treatment or to provide a signature to show which patients will develop fibrosis and end-organ damage. A recent review article in the Lancet emphasized the key need for more accurate biomarkers to understand prognosis and guide therapy in sarcoidosis.³ ACE levels are elevated in 60% of patients with sarcoidosis; however, the value of serum ACE levels in diagnosing or managing sarcoidosis lacks sensitivity and specificity.³ Hence studies have focused on finding new biomarkers to assess disease activity; neopterin and especially soluble interleukin-2 receptor (sIL-2R)

levels have been shown to be significantly elevated in active disease.^{25–27} Furthermore it has recently been shown that biomarkers sIL2 and s-ACE most often are not elevated in isolated CS.²⁸ Although promising, none of these new biomarkers is ready for clinical use. Very recently, highly sensitive troponin T (hsTnT) and (hsTnI) assays have been developed to improve the accuracy for detecting very low levels of biomarkers. In 2015, Kandolin et al. measured highly sensitive troponin levels in 62 patients with new-onset CS.²⁹ Thirty-three patients showed elevated concentrations at presentation; in 67% of cases, these normalized after steroid use for 4 weeks. In this study, we will assess the sensitivity, specificity and diagnostic accuracy of sIL-2R, hsTnI and novel biomarkers to detect and follow activity of CS.

Both sarcoidosis and its treatment with steroids may worsen quality of life (QoL). Judson et al.¹⁷ examined the effects of sarcoidosis and corticosteroid therapy on QoL in sarcoidosis outpatients. Patients were divided into those that received <500 mg of prednisone versus >500 mg of prednisone over the previous year. A multivariate analysis was performed using a propensity score analysis adjusted for race, age, gender and the severity of sarcoidosis. Patients who received <500 mg of prednisone in the previous year had an improved QoL compared to patients receiving >500 mg after adjusting for severity of illness. The authors concluded that these data support the search for effective alternative medications to corticosteroids.¹⁷ The generic and disease-specific QoL secondary endpoints evaluated in this trial will contribute significantly to our management of complex cardiac sarcoidosis patients, enabling physicians to make data-driven decisions not only to prolong life, but to improve the day-to-day quality of life that is of paramount importance to patients.

Potential limitations of the trial design primarily relate to the selection of the primary endpoint and the inferiority margins. Clinically manifest CS is a rare disease so we had to choose an imaging surrogate endpoint as the sample size would be too large with clinical endpoints. Hence the final choice of the primary endpoint and of the inferiority margin is based primarily on expert opinion and were a consensus of the steering committee; both are a compromise between ideal and what is practical. Within the study we hope to learn much more about many aspects of the disease including the clinical significance of the primary endpoint.

In addition to the listed goals of the trial, we will also establish a multi-center, multinational cardiac sarcoidosis clinical trials network. Such a collaborative infrastructure will enable a new era of high quality data to guide physicians when treating challenging cardiac sarcoidosis patients. We also aim to validate summed perfusion rest score as a viable surrogate for future trials. While this study focuses on the two most commonly used therapies for CS, corticosteroids and methotrexate, we envisage that this will be the first of a program of trials. A targeted, well-tolerated treatment would bring about a much-needed paradigm shift in the field of CS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Study flow diagram for the CHASM CS-RCT. Methotrexate will be initiated at 15 mg once weekly and increased to 20 mg after 4 weeks if tolerated.

Table 1.**Inclusion and Exclusion Criteria for CHASM CS-RCT Eligibility.**

Inclusion Criteria	Exclusion Criteria
<p>i. Cardiac sarcoidosis presenting with one or more of the following clinical findings:</p> <ul style="list-style-type: none"> a. advanced conduction system disease, defined as sustained (> 30 seconds) Mobitz II AV block or third degree AV block b. non-sustained or sustained ventricular arrhythmia c. left ventricular dysfunction (LVEF <50%) d. right ventricular dysfunction (RVEF <40%) <p>AND</p> <p>ii. No alternative explanation for clinical features</p> <p>AND</p> <p>iii. FDG-PET uptake suggestive of active CS within 2 months of enrollment</p> <p>AND</p> <p>iv. Abnormal FDG uptake in regional lymph nodes in a pattern consistent with sarcoidosis</p> <p>AND ONE OR BOTH OF THE FOLLOWING:</p> <p>v. Positive biopsy for sarcoid (endomyocardial or extra-cardiac)</p> <p>vi. CT chest showing features consistent with pulmonary sarcoidosis and/or hilar lymphadenopathy</p>	<p>Current or recent (within two months) non-topical treatment for sarcoidosis Currently taking Methotrexate or Prednisone for another health condition Intolerance or contra-indication to Methotrexate or Prednisone Patient does not meet all of the above listed inclusion criteria. Patient is unable or unwilling to provide informed consent. Patient is included in another randomized clinical trial. Patient has a contraindication to PET imaging or is unlikely to tolerate due to severe claustrophobia</p> <p>Pregnancy (all women of child bearing age and potential will have a negative BHCG test before enrollment)</p> <p>Breastfeeding</p> <p>Women of childbearing age who refuse to use a highly effective and medically acceptable form of contraception (IUD, sterilization, birth control implant or birth control pill) throughout the study.</p> <p>Patients for whom the investigator believes that the trial is not in the interest of the patient.</p>

Table 2.

Secondary endpoints for CHASM CS-RCT.

Secondary Endpoints	
1	Mortality
2	Cardiovascular hospitalization
3	Cardiac transplantation and/or implantation of a Left ventricular Assist Device
4	Medication related adverse events. All adverse events will be reported to coordinating center and relationship to study medication will be adjudicated by events committee.
5	Modified Cleveland Clinic Glucocorticoid Toxicity Score
6	Glucocorticoid Toxicity Index (GTI)
7	Patient reported symptoms related to medication
8	Medication compliance (% of days where treatment was taken as prescribed).
9	Generic and disease specific QOL.
10	Generic QOL will be assessed using SF 36.
11	Disease specific QOL will be assessed using the Kings Sarcoidosis Questionnaire (KSQ) and the Sarcoidosis Assessment Tool (SAT).
12	Weight and BMI at 6 months (absolute and delta compared to baseline)
13	Blood pressure at 6 months (absolute and delta compared to baseline)
14	HbA1C at 6-months (absolute and delta compared to baseline)
15	T-score on bone density scan (BMD) at 6 months (absolute and delta compared to baseline)
16	Additional FDG-PET and myocardial perfusion endpoints <ul style="list-style-type: none"> i. Summed perfusion rest score (SPRS) in mismatched segments i.e. segments with abnormal perfusion and increased FDG uptake.²⁴ ii. LV and RV FDG uptake on 6-month scan (absolute and delta compared to baseline). iii. Extra-cardiac disease activity on whole body FDG-PET scan at 6-months iv. LVEF and RVEF assessed on 6-month cardiac PET (absolute and delta compared to baseline).
17	Ventricular arrhythmia burden defined as episodes of sustained ventricular arrhythmia or episodes requiring appropriate ICD therapy (shock or anti-tachycardia pacing).
18	Percentage of patients who are in complete heart block at 6-month FU.
19	LVEF and RVEF assessed on 6-month echocardiogram (absolute and delta compared to baseline).
20	Highly sensitive Troponin I and BNP levels at 6-months (absolute and delta compared to baseline)
21	CMR endpoints <ul style="list-style-type: none"> i. Volume of Delayed Enhancement on patients who had CMR (absolute and delta compared to baseline) ii. Quantification of T2 on patients who had CMR (absolute and delta compared to baseline)