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Japanese Antibacterial Drug Management for Cardiac Sarcoidosis (J-ACNES): A multicenter, open-label, randomized, controlled study

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Abstract

Background: Cardiac sarcoidosis (CS) is a noncaseating granulomatous disease of unknown etiology. Lifelong immunosuppressive therapy, most frequently using corticosteroids, is a standard therapy to control hypersensitivity of immune reactions and prevent inflammation. However, it sometimes causes various systemic adverse effects and requires dose escalation. Thus, additional therapy may be required for the treatment of this disease. Recently, *Propionibacterium acnes* (*P. acnes*) was reported as one of the etiologic agents of CS, indicating that antibacterial drugs (ABD) may be effective for the treatment of CS. The objective of this study was to investigate the effect of ABD treatment, in addition to standard corticosteroid therapy, in patients with CS.

Methods: The Japanese Antibacterial Drug Management for Cardiac Sarcoidosis (J-ACNES) trial was designed as a prospective, multicenter, randomized, open-label, controlled clinical trial. The patients will be randomized to receive either standard corticosteroid therapy plus ABD therapy (ABD group) or standard corticosteroid

therapy (standard group). The primary endpoint is change in the total standardized uptake value at 6 months vs baseline using fluorine-18 fluorodeoxyglucose positron emission tomography and computed tomography. Secondary endpoints include efficacy, prognosis, and safety.

Results: The results of this study are currently under investigation.

Conclusion: The J-ACNES trial will be the first prospective study assessing the clinical benefit and safety of ABD therapy, in addition to corticosteroid treatment, in patients with CS. Our findings may improve treatment of patients with CS, as additional ABD therapy reduces recurrence of inflammation and elucidates the mechanism of sarcoidosis.

KEYWORDS
antibacterial drug, cardiac sarcoidosis, corticosteroid therapy, *Propionibacterium acnes*

1 | INTRODUCTION

Sarcoidosis is a systemic inflammatory and noncaseating granulomatous disease, involving various organs such as the lungs, eyes, heart, skin, lymph node, and nerves.[1] Although the etiology of sarcoidosis remains unknown, a hypersensitivity of immune reaction has been suspected as the main cause of sarcoidosis.[2] Cardiac sarcoidosis (CS) has been reported more frequently in Japan compared with other countries.[3,4] CS is an important predictor of poor prognosis in sarcoidosis due to advanced heart failure and various severe fatal arrhythmias such as atrioventricular block, ventricular tachycardia, and ventricular fibrillation.[5–10]

The standard treatment for CS involves immunosuppressive therapy with corticosteroids, administered to control the hypersensitivity of immune reaction,[11,12] prevent inflammation and fibrosis, and protect from deterioration of cardiac function. Previous studies revealed that long-term treatment with corticosteroids exerts a favorable effect on CS,[13] whereas discontinuation of corticosteroid therapy results in poor prognosis for CS.[14] Therefore, lifelong maintenance therapy with corticosteroids is recommended. Moreover, dose escalation of corticosteroids may be required due to worsening of inflammation in CS despite corticosteroid therapy. In 2015, a nationwide questionnaire survey involving 57 hospitals in Japan showed that the frequency of corticosteroid dose escalation was high (15.7%).[15] However, corticosteroids are associated with adverse effects including impaired glucose tolerance, osteoporosis, compromised host, and psychiatric effects. The occurrence of adverse effects is commonly dose-dependent. Thus, long-term maintenance therapy and dose escalation of corticosteroids in CS remain a challenge for treating physicians. Furthermore, additional immunosuppressive drugs such as methotrexate have been reported to be effective in corticosteroid-resistant patients with CS[16]; however, these data are limited. Therefore, alternative therapeutic options targeting the etiology of CS are necessary.

Eishi et al reported that *Propionibacterium acnes* (*P. acnes*) was present in the sarcoid lesions of patients with sarcoidosis.[17] Moreover, a study using an animal model showed that the eradication of indigenous *P. acnes* by antibacterial drugs (ABD) alleviated the granulomatous disease.[18] Furthermore, in patients with CS, *P. acnes* has been frequently identified in sarcoid granulomas of myocardial tissues.[19] These findings suggest that *P. acnes* may be an etiologic agent of CS, and ABD therapy against *P. acnes*, in addition to corticosteroid therapy, may be effective in these patients.

Therefore, we conducted an investigation of the effect of ABD, in addition to corticosteroid treatment, in patients with CS.

2 | METHODS

2.1 | Objective

The J-ACNES trial was designed as a prospective, multicenter, randomized, open-label, controlled clinical trial of additional ABD therapy for CS (UMIN Clinical Trials Registry UMIN 000025936). The objective of this trial was to investigate the clinical benefit and safety of ABD therapy, in addition to corticosteroid treatment, in patients with CS.

2.2 | Study design

The patients will be randomized in a 1:1 ratio to receive either standard corticosteroid therapy plus ABD therapy (ABD group) or standard corticosteroid therapy (standard group). The time course of this study is shown in Figure 1.

Randomization will be performed using a web-based validated system (tsClinical DDworks21/EDC plus, FUJITSU LIMITED, Japan), based on a minimization scheme with stratification by sex, age, left ventricular ejection fraction (LVEF), the presence of sustained ventricular tachycardia or ventricular fibrillation, and the presence of atrioventricular block.

The primary endpoint of this study is change in the total standardized uptake value (SUV) at 6 months vs baseline using fluorine-18 fluorodeoxyglucose positron emission tomography and computed

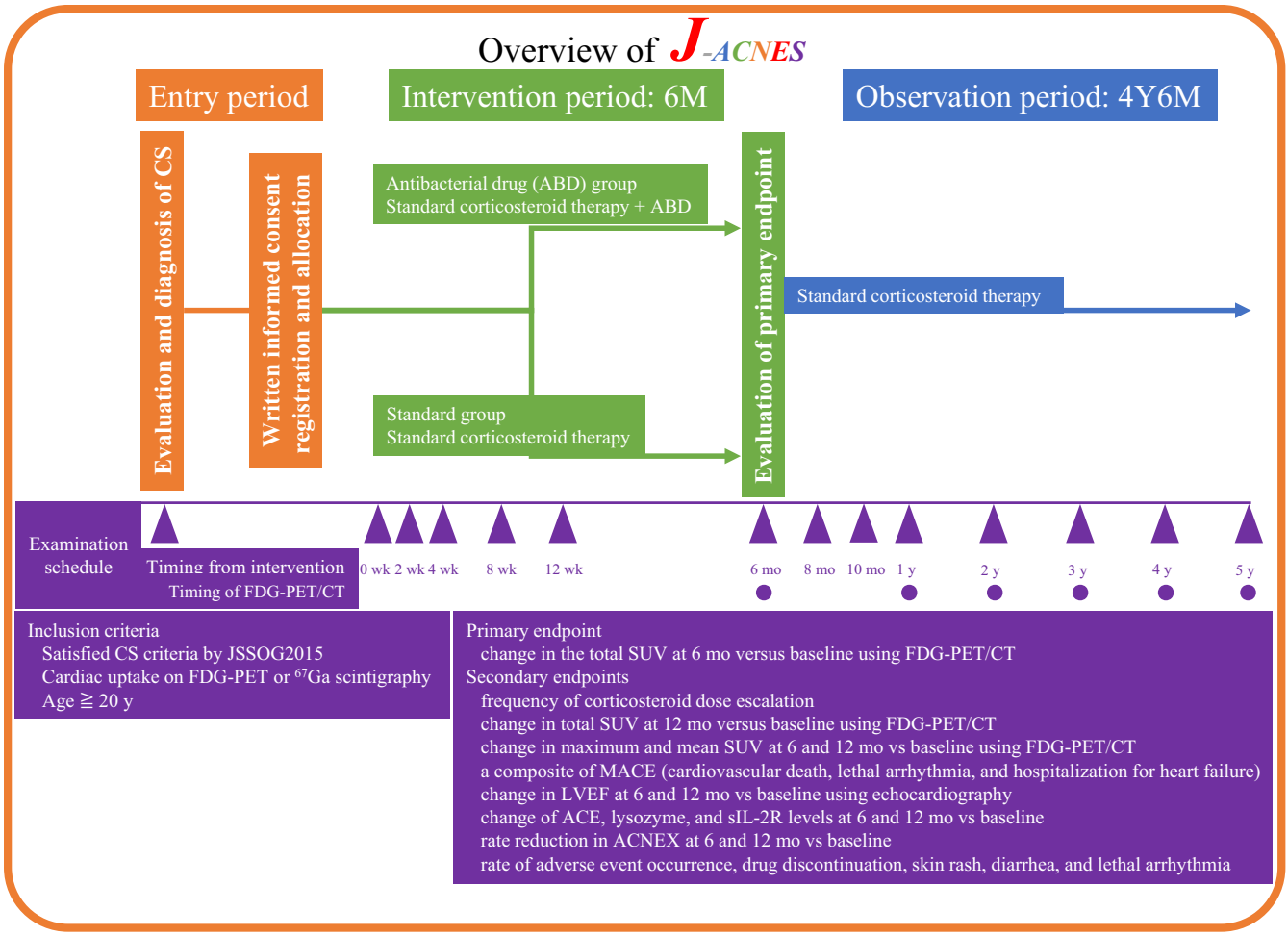

FIGURE 1 Overview of the J-ACNES trial. ACE, angiotensin-converting-enzyme, ABD, antibacterial drug, CS, cardiac sarcoidosis, FDG-PET/CT, fluorine-18 fluorodeoxyglucose positron emission tomography and computed tomography, JSSOG, Japanese Society of Sarcoidosis and Other Granulomatous disease, LVEF, left ventricular ejection fraction, M, month, N, number, sIL-2R, soluble interleukin-2 receptor, SUV, standardized uptake value, W, week, Y, year, ^{67} Ga, gallium-67

tomography (FDG-PET/CT). Secondary efficacy endpoints include the following: frequency of corticosteroid dose escalation at 6 and 12 months, change in total SUV at 12 months vs baseline using FDG-PET/CT, change in the maximum and mean SUV at 6 and 12 months vs baseline using FDG-PET/CT, a composite of major adverse cardiovascular events (MACE) (cardiovascular death, lethal arrhythmia, and hospitalization due to heart failure) within 6, 12, 36, and 60 months, cardiovascular death, lethal arrhythmia, and heart failure hospitalization within 6, 12, 36, and 60 months, change in LVEF at 6 and 12 months vs baseline using echocardiography, change in angiotensin-converting-enzyme (ACE) level, lysozyme level, soluble interleukin-2 receptor (sIL-2R) levels at 6 and 12 months vs baseline, and rate reduction in plasma *P. acnes* lipoteichoic acid concentration (ACNEX) at 6 and 12 months vs baseline. Safety endpoints include the frequency of adverse events and treatment discontinuation due to adverse events at 6 and 12 months, as well as the frequency of skin rash, diarrhea, and lethal arrhythmia at 6 and 12 months.

The study protocol must be approved by all participating institutions. All participants are required to provide written informed consent (M28-110, Dec 12, 2016).

2.3 | Study population

Patients with CS, in need of de novo corticosteroid therapy, will be enrolled in this study. Patient inclusion criteria are as follows: (i) CS criteria according to the Japanese Society of Sarcoidosis and Other Granulomatous disease (JSSOG) 2015 with cardiac histopathological findings or with histopathological findings of other organs (skin or lung) and clinical signs of cardiac involvement, (ii) male and female patients aged ≥20 years, and (iii) a cardiac abnormal uptake finding on FDG-PET or gallium-67 (^{67} Ga) scintigraphy. The exclusion criteria are as follows: (i) aged <20 years, (ii) severe heart failure with shock, and (iii) severe liver and renal dysfunction.

2.4 | Sample size calculation

As data regarding ABD therapy in addition to corticosteroid therapy for patients with CS are limited, it is not possible to predetermine the required sample size for this study. Thus, the study was designed to enroll a minimum of 80 patients and perform an interim analysis for sample size recalculation based on the observed data.

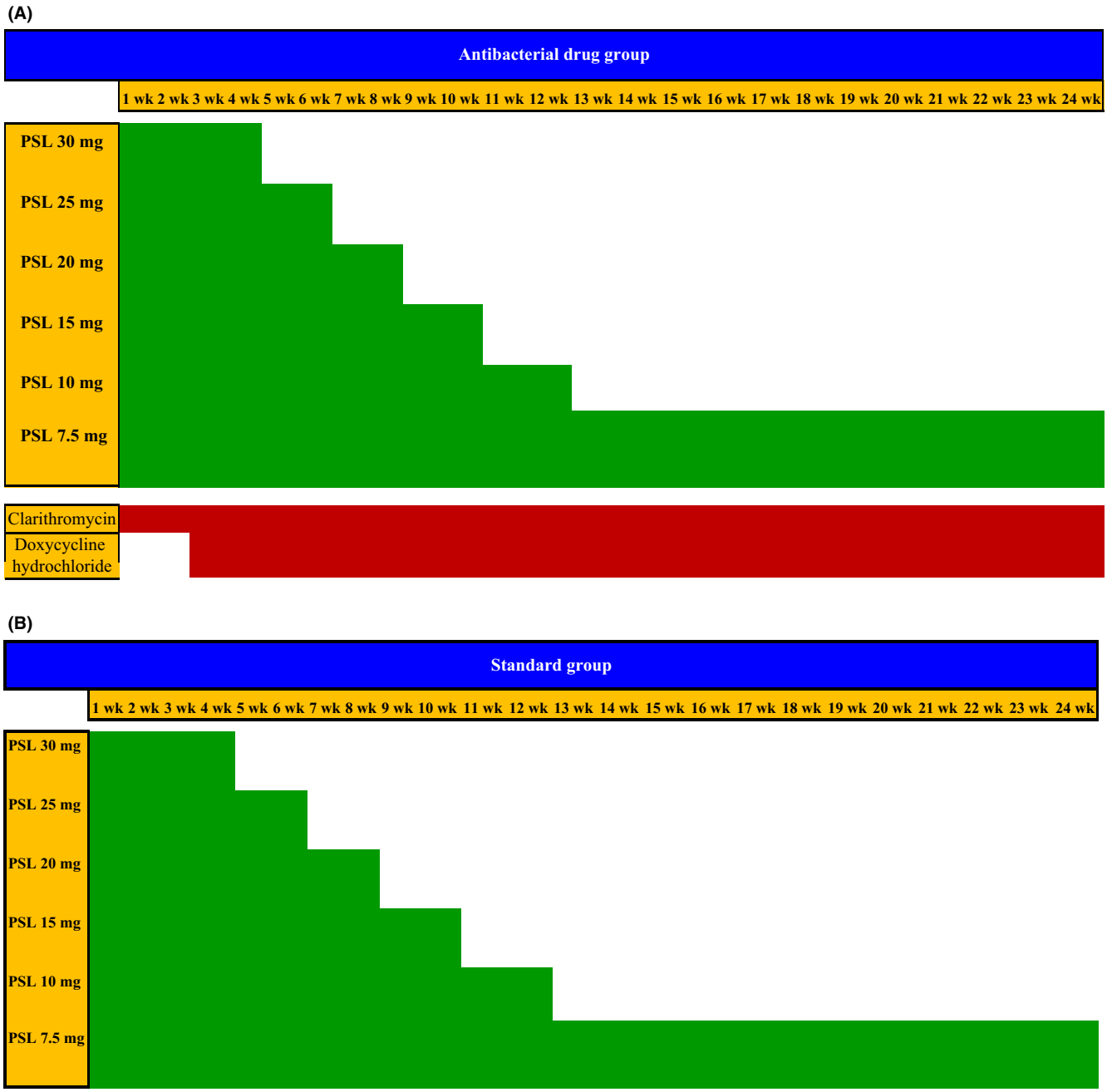

FIGURE 2 Sample of drug administration schedule (adjustment period: 2 wks). A, Schedule of drug administration in the ABD group for 24 wks, B, Schedule of drug administration in the standard group for 24 wks. ABD, antibacterial drug, PSL, prednisolone, W, week

2.5 | Drug administration

The schedule for the administration of ABD therapy is shown in Figure 2A. The initial daily dose of corticosteroid is 30 mg administered for 1 month. Thereafter, the dose is adjusted to 25, 20, 15, 10, and 7.5 mg (maintenance dose) every 2-4 weeks for the remainder of the study period. Clarithromycin (400 mg/day) is administered concurrently with initial administration of a corticosteroid for 24 weeks and is subsequently discontinued. Two weeks after administration of clarithromycin, doxycycline hydrochloride (100 mg/day) is administered in the ABD group to avoid adverse effects observed with the administration of clarithromycin. Administration of doxycycline hydrochloride is continued for 22 weeks and subsequently discontinued. The use of single ABD agents is allowed when adverse effects caused by another ABD agent occur.

The schedule for the administration of standard therapy is shown in Figure 2B. The administration of corticosteroid therapy is identical to that of the ABD group.

2.6 | Dose escalation of corticosteroid therapy

Dose escalation of corticosteroid therapy is based on the following criteria: (i) improvement of <10% in the maximum SUV at study visits vs baseline using FDG-PET/CT, (ii) decrease in ≥10% in LVEF at

follow-up vs baseline using echocardiography, (iii) thinning or thickening of the ventricular wall occurring or worsening using echocardiography, (iv) increase in serum markers (sIL-2R, ACE, and lysozyme), and (v) decision by the expert committee of this study.

2.7 | Study visits

Study visits will be scheduled at 2, 4, 8, 12, 24, 32, 40, and 48 weeks and at 2, 3, 4, and 5 years after administration of treatment. During these visits, drug management, standard blood examinations, 12-lead electrocardiograms, collection of data on the concomitant usage of drugs, recording of treatment-related adverse effects, and/or clinical events including MACE will be performed. Vital data and special blood examinations will be performed at 12 weeks. In addition, chest X-ray, echocardiography, 24-h Holter electrocardiogram (ECG) monitoring, and FDG-PET/CT will be performed at 24 and 48 weeks, and at 2, 3, 4, and 5 years.

2.8 | Evaluations

Patient baseline characteristics and the status of medical treatment for each group are shown in Table 1. Follow-up data for each group are presented in Table 2.

Data will be shared using only a specific ID number allocated to protect the identity of patients. The protocol of this study will be approved by the Ethics Committee of each institution and conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practices. Informed consent will be obtained from the patients and/or their legal guardians.

2.9 | Monitoring

At each visit, the principal investigator (PI) or investigator will interview the patient. When an adverse event occurs, the PI or investigator will follow up with the patient until the AE resolves and will input the data into the website.

In this trial, the data monitoring committee will perform a central monitoring of the data stored on the website. The data monitoring committee is independent of the investigators.

2.10 | Data quality control and management

The PI or investigator must follow the instructions of this study protocol. The PI and investigator cannot modify the protocol without permission by the ethics committees at each center. When a deviation from the protocol occurs, the PI or investigator must record everything.

When new data requiring revision of the protocol are identified and the data monitoring committee recommends the revision, the representative investigator of this trial will revise the protocol. The revision of the protocol must be approved by the ethics committees at each center.

TABLE 1 Patient baseline characteristics and status of medical treatment in the J-ACNES trial

Age, years
Male sex, n (%)
Body height, cm
Body weight, kg
Vital data
Blood pressure, mmHg
Heart rate, bpm
Standard blood examination
WBC, Hb, platelet, total protein, albumin, AST, ALT, creatinine, LDH, calcium, sodium, potassium,CRP, FBS, HbA1c
Special blood examination
ACE, lysozyme, sIL-2R, BNP, FT4, TSH, ACNEX (Plasma *P. acnes* lipoteichoic acid concentration)
12-lead electrocardiograms
Heart rate, bpm, pacing wave, n (%), atrioventricular block, n (%), atrial fibrillation and/or atrial flutter, n (%), ventricular tachycardia, n (%), other abnormal findings, n (%)
Chest X-ray
Bilateral hilar lymphadenopathy, n (%), other abnormal findings, n (%)
Echocardiography
LVEF, %, left ventricular end-diastolic diameter, mm, left ventricular end-systolic diameter, mm, ventricular wall thickness, mm, ventricular aneurysm, n (%)
24-h Holter ECG monitoring
Ventricular tachycardia, n (%), mean heart rate, bpm, max heart rate, bpm, minimum heart rate, bpm, premature ventricular contraction, n (%), premature supraventricular contraction, n (%), atrial fibrillation, n (%), atrioventricular block, n (%), sinus pause ≧2.5 s, n (%)
FDG-PET/CT
Maximum SUV
Integrated intensity by Bull's-eye plot analysis
Mean SUV, total SUV, the dispersion value of SUV, the coefficient of variation in SUV
Concomitant drug use
ACE inhibitor and/or ARB, n (%), beta blocker, n (%), anti-arrhythmic drug, n (%), antihypertensive drug, n (%), other kind of drug, n (%)
Combination therapy
Pacemaker, n (%), ICD, n (%), CRT-P, n (%), CRT-D, n (%), other combination therapy, n (%)

ACE, angiotensin-converting-enzyme; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; CRP, C-reactive protein; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; ECG, electrocardiogram; FBS, fasting blood sugar; FDG-PET/CT, fluorine-18 fluorodeoxyglucose positron emission tomography and computed tomography; FT4, free thyroxine; Hb, hemoglobin; ICD, implantable cardioverter-defibrillator; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; sIL-2R, soluble interleukin-2 receptor; SUV, standardized uptake value; TSH, thyroid stimulating hormone; WBC, white blood cell.

TABLE 2 Study visit data of the J-ACNES trial

Vital data, standard blood examination, special blood examination, 12-lead electrocardiograms, chest X-ray, echocardiography, 24-h Holter ECG monitoring, FDG-PET/CT,
Same evaluation items for Table 1
Drug management (corticosteroid and antibacterial drugs)
Drug daily dose, mg
Change in drug dose, n (%)
Dose reduction, n (%), dose escalation, n (%), change date, reason of change
Drug discontinuation, n (%)
Discontinuation date, reason for discontinuation
Medication compliance, n (%)
Compliance rate ≧120%, 120 ≫ 80%, ≧80%
Adverse effect
Skin rash, n (%)
Occurrence date, severity, association with drug, outcome
Diarrhea, n (%)
Occurrence date, severity, association with drug, outcome
Lethal arrhythmia, n (%)
Type of lethal arrhythmia, occurrence date, severity, association with drug, outcome
Other adverse effect, n (%)
Type of adverse effect, occurrence date, severity, association with drug, outcome
Clinical outcome
Mortality, n (%)
Cause of death, date of death
Cardiovascular death, n (%)
Lethal arrhythmia, n (%)
Type of lethal arrhythmia, occurrence date, detail information of lethal arrhythmia
Heart failure hospitalization, n (%)
Cause of heart failure worsening, admission date, detail information of heart failure worsening
Improvement of skin sarcoidosis, n (%)
Detail information of skin sarcoidosis
Improvement of lung sarcoidosis, n (%)
Detail information of lung sarcoidosis
Other clinical event, n (%)
Type of clinical event, occurrence date, detail information of other clinical event
Dose escalation of corticosteroid, n (%)
Date of dose escalation, dose after dose escalation, reason of dose escalation

ECG, electrocardiogram; FDG-PET/CT, fluorine-18 fluorodeoxyglucose positron emission tomography and computed tomography.

2.11 | Statistical analysis

Data will be summarized using descriptive statistics (mean or median and standard deviation or percentiles for continuous variables, frequencies and percentages for categorical variables). For the primary endpoint, the mean difference and the 95% confidence interval between the treatment groups will be estimated using analysis of covariance, with baseline SUV as a covariate. The per-protocol analysis will be performed as a secondary analysis. Subgroup analyses will be conducted to investigate differential effects of intervention such as age (<60 years vs ≥60 years), sex, and baseline LVEF (<40% vs ≥40%). Secondary endpoints will be assessed using Student's *t* test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. The occurrence of events will be estimated using the Kaplan-Meier method and compared between treatment groups using the log-rank test. The hazard ratio and the 95% confidence interval will be calculated using the Cox proportional-hazards model.

An interim analysis will be performed at the time of primary endpoint observation in 60 patients, for sample size recalculation based on the conditional power.[20] At the final analysis, the efficacy will be assessed using the inverse normal method[21,22] for controlling the rate of type I error.

The detailed plan for the interim and final analyses will be prespecified in the statistical analysis plan, which will be prepared prior to database lock.

3 | RESULTS

The results of this study are currently under investigation.

4 | DISCUSSION

In the J-ACNES trial, ABD combination therapy will be added to corticosteroid therapy for patients with CS. Treatment of granulomatous disease is commonly conducted using multidrug combination therapy. Standard therapy for tuberculosis involves multidrug combination therapy for 6 months, that is, combination therapy of 4 drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol) for 2 months and combination of 2 drugs (rifampicin and isoniazid) for 4 months. Standard therapy for leprosy involves the combination of 3 drugs (rifampicin, diaminodiphenyl sulfone, and clofazimine) for a duration of 6 to 12 months. Thus, the duration of ABD therapy in the present study (6 months) is in accordance with the current treatment strategy for granulomatous disease.

In the present study, clarithromycin and doxycycline hydrochloride will be used as ABD therapy for CS. Previous studies have demonstrated that clarithromycin, doxycycline hydrochloride, and minocycline were effective in patients with CS.[23–25] However, monotherapy with antibacterial agents was insufficient for the treatment of CS.[26] It has been shown that the frequency of adverse effects of doxycycline hydrochloride was lower than that of minocycline.[27] Previous treatment of patients with CS using clarithromycin (200-400 mg/day) and doxycycline hydrochloride (100-200 mg/day) has shown a good safety profile in these patients. Thus, clarithromycin (400 mg/day) and doxycycline hydrochloride (100 mg/day) administered in this trial may be an appropriate dose for the treatment of CS.

The appropriate combination pattern, administration period, and frequency of adverse effects of ABD therapy for CS remain unclear. Therefore, the efficacy and safety of ABD therapy, in addition to corticosteroid therapy, for the treatment of CS are assessed in this study.

5 | CONCLUSION

The J-ACNES trial will be the first prospective investigation assessing the clinical benefit and safety of ABD therapy, in addition to corticosteroid therapy, for the treatment of patients with CS. These findings may improve the treatment of patients with CS, as additional ABD therapy reduces the recurrence of inflammation and elucidates the mechanism of sarcoidosis.

CONFLICT OF INTEREST

Authors declare no conflict of interests for this article.

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