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

Kohei Ishibashi MD, PhD1 | Yoshinobu Eishi MD, PhD2 | Nobuhiro Tahara MD, PhD3 | Masanori Asakura MD, PhD4 | Naka Sakamoto MD, PhD5 | Kazufumi Nakamura MD, PhD6 | Yoichi Takaya MD, PhD6 | Tomohisa Nakamura MD, PhD3 | Yoshikazu Yazaki MD, PhD7 | Tetsuo Yamaguchi MD, PhD8 | Koko Asakura PhD11 | Toshihisa Anzai MD, PhD9 | Teruo Noguchi MD, PhD1 | Satoshi Yasuda MD, PhD1 | Fumio Terasaki MD, PhD10 | Toshimitsu Hamasaki PhD11 | Kengo Kusano MD, PhD1

1Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan
2Department of Human Pathology, Tokyo Medical and Dental University, Tokyo, Japan
3Department of Cardiovascular Medicine, Kurume University, Fukuoka, Japan
4Department of Cardiovascular Medicine, Hyogo College of Medicine, Hyogo, Japan
5Department of Cardiovascular Medicine, Asahikawa Medical University, Hokkaido, Japan
6Department of Cardiovascular Medicine, Okayama University, Okayama, Japan
7Department of Cardiovascular Medicine, Saku Central Hospital, Nagano, Japan
8Department of Respiratory Medicine, Shinjuku Kaiso Bldg. Clinic, Tokyo, Japan
9Department of Cardiovascular Medicine, Hokkaido University, Hokkaido, Japan
10Medical Education Center/Department of Cardiology, Osaka Medical College, Osaka, Japan
11Department of Data Science, National Cerebral and Cardiovascular Center, Osaka, Japan

Correspondence
Kengo Kusano, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan. Email: kusanokengo@hotmail.com

Funding Information
The J-ACNES trial is supported by Daiichi Sankyo Company and Grant-in-Aid for Scientific Research (18k080920019).

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. Although the etiology of sarcoidosis remains unknown, a hypersensitivity of immune reaction has been suspected as the main cause of sarcoidosis. Cardiac sarcoidosis (CS) has been reported more frequently in Japan compared with other countries. 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.

The standard treatment for CS involves immunosuppressive therapy with corticosteroids, administered to control the hypersensitivity of immune reaction, 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, whereas discontinuation of corticosteroid therapy results in poor prognosis for CS. 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%). 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; 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. Moreover, a study using an animal model showed that the eradication of indigenous P. acnes by antibacterial drugs (ABD) alleviated the granulomatous disease. Furthermore, in patients with CS, P. acnes has been frequently identified in sarcoid granulomas of myocardial tissues. 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...
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 MACE (cardiovascular death, lethal arrhythmia, and hospitalization for heart failure) within 6, 12, 36, and 60 months, change in LVEF at 6 and 12 months vs baseline using echocardiography, change in ACE, lysozyme, and sIL-2R levels at 6 and 12 months vs baseline, rate reduction in ACNEX at 6 and 12 months vs baseline, rate of adverse event occurrence, drug discontinuation, skin rash, diarrhea, and lethal arrhythmia.

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 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.
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 concomitant usage of drugs, recording of treatment at each center.

When new data requiring revision of the protocol are identified by the ethics committees at each center. When a deviation from the protocol occurs, the PI or investigator must record everything. The PI or investigator must follow the instructions of this study protocol. The representative investigator of this trial will revise the protocol. The data monitoring committee recommends the revision, the PI or investigator must record everything. When a deviation from the protocol occurs, the PI or investigator must record everything. The PI or investigator cannot modify the protocol without permission from the ethics committees at each center. When a deviation from the protocol occurs, the PI or investigator must record everything.

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 from 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, ACNES (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 (%) |
| 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; ASAT, 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 method21,22 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.

ORCID

Toshimitsu Hamasaki http://orcid.org/0000-0002-4928-1160
Kengo Kusano http://orcid.org/0000-0002-5760-9285

REFERENCES

1. Kusano KF, Satomi K. Diagnosis and treatment of cardiac sarcoidosis. Heart. 2016;102:184–90.
2. Gerke AK, Hunninghake G. The immunology of sarcoidosis. Clin Chest Med. 2008;29:379–90, vii.
3. Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med. 2001;164:1885–9.
4. Iwai K, Sekiguti M, Hosoda Y, et al. Racial difference in cardiac sarcoidosis incidence observed at autopsy. Sarcoidosis. 1994;11:26–31.
5. Roberts WC, McAllister HA Jr, Ferrans VJ. Sarcoidosis of the heart. A clinicopathologic study of 35 necropsy cases (group 1) and review of 78 previously described necropsy patients (group 11). Am J Med. 1977;63:86–108.
6. Yazaki Y, Isobe M, Hiroe M, et al. Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. Am J Cardiol. 2001;88:1006–10.
7. Sekiguchi M, Hiroe M, Take M, Hirozawa 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;44:264.
8. Takahashi K, Okumura Y, Watanabe I, et al. A case of cardiac sarcoidosis presenting with double tachycardia. J Arrhythm. 2015;31:58–9.
9. Banba K, Kusano KF, Nakamura K, et al. Relationship between arrhythmogenesis and disease activity in cardiac sarcoidosis. Heart Rhythm. 2007;4:1292–9.
10. Takaya Y, Kusano K, Nishi N, Nakamura K, Ito H. Early and frequent defibrillator discharge in patients with cardiac sarcoidosis compared with patients with idiopathic dilated cardiomyopathy. Int J Cardiol. 2017;240:302–6.
11. Takaya Y, Kusano KF, Nakamura K, 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;176:522–5.
12. Grutters JC, van den Bosch JM. Corticosteroid treatment in sarcoidosis. Eur Respir J. 2006;28:627–36.
13. Kandolin R, Lehtonen J, Airaksinen J, et al. Cardiac sarcoidosis: epidemiology, characteristics, and outcome over 25 years in a nationwide study. Circulation. 2015;131:624–32.
14. Nagai T, Nagano N, Sugano Y, 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;117:966–71.
15. Nagayama T, Ishibashi K, Kamakura T, et al. Long time clinical course of cardiac sarcoidosis: retrospective analysis in Japan. Eur Heart J. 2016;37(Abstract Supplement):1010.
16. Nagai S, Yokomatsu T, Tanizawa K, et al. Treatment with methotrexate and low-dose corticosteroids in sarcoidosis patients with cardiac lesions. Intern Med. 2014;53:427–33.
17. Ishige I, Usui Y, Takemura T, Eishi Y. Quantitative PCR of mycobacterial and propionibacterial DNA in lymph nodes of Japanese patients with sarcoidosis. Lancet. 1999;354:120–3.
18. Nishiwaki T, Yoneyama H, Eishi Y, et al. Indigenous pulmonary Propionibacterium acnes primes the host in the development of sarcoïd-like pulmonary granulomatosis in mice. Am J Pathol. 2004;165:631–9.
19. Asakawa N, Uchida K, Sakakibara M, et al. Immunohistochemical identification of Propionibacterium acnes in granuloma and inflammatory cells of myocardial tissues obtained from cardiac sarcoidosis patients. PLoS ONE. 2017;12:e0179980.
20. Lan K, Simon R, Halperin M. Stochastically curtailed tests in long term clinical trials. Communications in Statistics. Seq Anal. 1982;1:207–19.
21. Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. Biometrics. 1999;55:1286–90.
22. Cui L, Hung H, Wang S. Modification of sample size in group sequential clinical trials. Biometrics. 1999;55:853–7.
23. Bachelez H, Senet P, Cadranel J, Kaoukhov A, Dubertret L. The use of tetracyclines for the treatment of sarcoidosis. Arch Dermatol. 2001;137:69–73.
24. Oritsu M. The experience of antibacterial drug for sarcoidosis (Japanese nationwide survey). Health Labour Sciences Research Grant Research Report. 2005:210–3.
25. Yamaguchi T, Zaima M, Yamada K, et al. Tetracycline therapy for sarcoidosis. J Jpn Soc Sarcoidosis Other Granulomatous Dis. 2008;28:41–7.
26. Hiraga Y, Omichi M, Yamada G. The effect of antibacterial drug for sarcoidosis. Ministry of Health and Welfare specific disease diffuse lung disease research team research report. 1995:174–5.
27. Yamaguchi T, Yamaguchi Y, Suzuki M, Kawano C, Yamada K. Doxycycline therapy for sarcoidosis. J Jpn Soc Sarcoidosis Other Granulomatous Dis. 2014;34:31–3.

How to cite this article: Ishibashi K, Eishi Y, Tahara N, et al. Japanese Antibacterial Drug Management for Cardiac Sarcoidosis (J-ACNES): A multicenter, open-label, randomized, controlled study. J Arrhythmia. 2018;34:520–526. https://doi.org/10.1002/joa3.12084