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Letters

RESEARCH LETTER

Prognostic Implication of the Resolution of Myocardial FDG Uptake in Patients With Cardiac Sarcoidosis

Cardiac sarcoidosis (CS) determines the prognosis of patients with systemic sarcoidosis. Management of CS follows a guideline-directed medical therapy for heart failure based on ejection fraction and immunosuppressive therapy. Additionally, the European Association of Cardiovascular Imaging and the American Society of Nuclear Cardiology proposed undergoing ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT) at the time of diagnosis to provide prognostic information and assessment of therapeutic response of immunosuppressive agents in CS; however, the association between resolution of abnormal myocardial FDG uptake and prognosis in patients with CS has not been well elucidated.

ILLUMINATE-CS (Illustration of the Management and Prognosis of Japanese Patients With Cardiac Sarcoidosis) was a retrospective registry of patients with CS diagnosed from 2001 to 2017.[1]

From this registry, we included patients who underwent FDG-PET before starting immunosuppressive treatment and at least once after the achievement of the maintenance dose of steroid, which was defined as prescribing the same dose 3 times in a row after starting steroid taper. The most recently acquired image after the achievement of the maintenance dose was used. The American Heart Association 17-segment model was used to evaluate the myocardium showing FDG uptake on PET/CT. ^{18}F-FDG (185 MBq) was injected intravenously after at least 12 hours of fasting to minimize physiologic myocardial FDG uptake in all participating institutions.

The improvement in uptake in the heart (PET improvement [PETIMP]) was defined as follows: patients with myocardial segments with FDG uptake at baseline and those segments decreased from baseline and to ≤1 segment at follow-up scanning. The study population was divided based on the occurrence of PETIMP to investigate its impact on clinical outcomes. The primary endpoint was all-cause death. All data were retrospectively obtained from medical records. The period of follow-up was from diagnosis of CS to final visit or the occurrence of death. The adjustment of steroid dose depended on the attending physicians.

This study complied with the Japanese Ethical Guidelines for Medical and Health Research involving Human Subjects and the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of each participating hospital, and informed consent was waived because of the retrospective nature of the study. Study information was published in the publicly available University Hospital Information Network (UMIN000034974).

Data were analyzed using JMP 16 software (SAS Institute, Inc). Kaplan-Meier analysis with log-rank test was used to compare the survival curves between the groups. Univariate and multivariate Cox proportional hazards models were used to estimate the HRs and 95% CIs for the association between each variable and the incidence of all-cause death. As for multivariate Cox analysis, age, sex, left ventricular ejection fraction, and B-type natriuretic peptide levels were used as adjustment variables to evaluate the association between PETIMP and prognosis based on previous findings from ILLUMINATE-CS and the literature.[1] Considering the limited number of patients who reached the primary endpoint, the least absolute shrinkage and selection operator (LASSO) regression analysis was performed as a sensitivity analysis to determine the significant predictors for all-cause death using 10-fold cross validation.

A total of 186 patients who met the criteria showed FDG uptake at least in 1 segment at baseline. Consequently, 113 patients were identified as the PETIMP group. Follow-up PET was performed at a median of 488 days (IQR: 216-1,090 days) from the time of baseline. The prescription rates of steroids were similar in patients with and without PETIMP (94.7% vs 98.6%; $P = 0.14$). The prednisolone-equivalent steroid maintenance dose was not significantly different in both groups (7.5 ± 3.7 mg vs 7.3 ± 3.3 mg; $P = 0.76$). At baseline, the number of myocardium

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FIGURE 1 Cox Proportional Analysis and LASSO Regression Analysis for All-Cause Mortality

A Cox proportional hazards ratio of PETIMP for all-cause mortality

	Hazard ratio	95% confidence intervals		P Value
PETIMP (unadjusted)	0.07	0.01	0.49	0.008
PETIMP (adjusted by age, male sex, log BNP, and LVEF)	0.08	0.01	0.70	0.02

B LASSO regression analysis for all-cause death

Variables	Coefficient
Diabetes	0.19
Usage of beta blocker	0.46
PETIMP	-1.19
Atrial fibrillation	2.39
Log BNP	-0.04

(A) Cox proportional hazards ratio of PETIMP for all-cause mortality. **(B)** LASSO regression analysis for all-cause death. Male sex, extracardiac involvement, hypertension, diabetes, history of heart failure admission, ventricular tachycardia/ventricular fibrillation, atrioventricular block, atrial fibrillation, New York Heart Association functional class ≥ III, use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, use of beta blocker, PET improvement (PETIMP), age, creatinine, B-type natriuretic peptide (BNP), angiotensin-converting enzyme, and steroid maintenance dose were included in the LASSO regression analysis. PETIMP was defined as patients with myocardial segments with FDG uptake at baseline and those segments decreased from baseline and to ≤1 segment at follow-up scanning. LASSO = least absolute shrinkage and selection operator.

segments with FDG uptake in PET/CT was 4 segments (IQR: 2-8 segments) in patients with PETIMP and 6 segments (IQR: 4-8 segments) in those without PETIMP ($P = 0.28$).

During a median follow-up period of 884 days (IQR: 485-1,563 days), 1 patient with PETIMP and 10 patients without PETIMP died (0.9% vs 13.7%; log-rank $P = 0.001$ in Kaplan-Meier analysis). In the unadjusted (HR: 0.06; 95% CI: 0.01-0.49; $P = 0.008$) and adjusted Cox hazard models (HR: 0.08; 95% CI: 0.01-0.70; $P = 0.02$), PETIMP was associated with lower mortality. In the least absolute shrinkage and selection operator regression analysis, PETIMP was a predictor for all-cause death (Figure 1).

This subanalysis resulted in 2 main findings. First, 113 patients who received conventional therapy including steroids had resolution of FDG uptake (60.8%). Because of the paucity of data for serial FDG changes in patients with CS, our finding provides important data for the association between the conventional management of patients with CS and resolution of myocardial FDG uptake. Second, all-cause mortality was significantly lower in patients with PETIMP than in those without PETIMP (log-rank $P = 0.001$). Resolution of myocardium FDG uptake after achieving the maintenance steroid dose may predict prognosis in patients with CS. Further investigations are needed to confirm these findings.

The optimal timing of PET/CT follow-up has not been determined. Universal scanning methods and quantitative evaluation of PET/CT for patients with CS are needed for future research.

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