Brief Report

Serial Cardiac FDG-PET for the Diagnosis and Therapeutic Guidance of Patients With Cardiac Sarcoidosis

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ABSTRACT

Background: Cardiac fluorodeoxyglucose positron-emission tomography (FDG-PET) has emerged as a standard imaging modality for the diagnosis of cardiac sarcoidosis (CS); however, there is a scarcity of data on the use of serial FDG-PET to guide immunosuppressive therapy. The aim of this work was to report our experience using serial FDG-PET for the diagnosis and management of patients with CS, focusing on its utility in ongoing immunosuppression management.

Methods and Results: We studied consecutive patients with CS managed at Stanford University from 2010 to 2017. We evaluated our experience using FDG-PET for diagnosis and guidance of immunosuppressive therapy titration in CS. Among 34 patients diagnosed with CS, 16 (47%), 12 (35%) and 14 (41%) presented with heart block, heart failure, and ventricular arrhythmias, respectively. FDG-PET proved beneficial in the initial diagnosis in 21 patients (62%). A total of 128 FDG-PET scans were performed (median 3 per patient). Ninety-four FDG-PET scans (73%) resulted in a change in therapy, with 42 FDG-PET scans (33%) instrumental for tapering prednisone. Among patients who were initiated on prednisone, the mean dose of prednisone at 1 year was 9.5 mg/d. Over a median follow-up of 2.3 years, 48% of patients were successfully weaned from prednisone completely, and 20% were weaned to a maintenance dosage of 5−10 mg/d. During the follow-up period, transplant-free survival was 88%.

Conclusions: The use of serial cardiac FDG-PET for the diagnosis and management of CS was critical for guiding immunosuppression management and resulted in low chronic steroid doses and good disease control within 1 year of diagnosis. (*J Cardiac Fail 2019;25:307−311*)

Key Words: Cardiac sarcoidosis, FDG-PET, image-guided therapy.

Sarcoidosis is a multiorgan inflammatory disease characterized by deposition of noncaseating granulomas. Higher prevalence is observed in northern Europeans and African-Americans, suggesting a genetic or environmental predisposition. Sarcoidosis can affect the myocardium, causing inflammation, edema, scarring, and remodeling. This can lead to conduction abnormalities, heart failure, ventricular arrhythmias, and sudden cardiac death.[1] Prompt diagnosis and treatment of cardiac sarcoidosis (CS) may limit inflammation and subsequent fibrosis. There is no currently Food and Drug Administration−approved therapy, but immunosuppressants, such as corticosteroids, methotrexate, and tumor necrosis factor alpha (TNF-α) inhibitors have been used. Other interventions include permanent pacemakers (PPMs), implantable cardioverter-defibrillators (ICDs), and cardiac transplantation.[1,2]

CS is substantially underdiagnosed according to autopsy studies, as compared with published prevalence.[2] Endomyocardial biopsy is not routinely performed owing to its invasiveness and poor sensitivity (20%−30%).[1,3] Gallium-67 scintigraphy was used previously but exhibited unreliable sensitivity, poor specificity, low image resolution, and

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Manuscript received June 13, 2018; revised manuscript received February 10, 2019; revised manuscript accepted February 22, 2019.

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1071-9164/$ - see front matter

https://doi.org/10.1016/j.cardfail.2019.02.018

high radiation exposure.[4] Emergence of advanced imaging technology, including fluorodeoxyglucose positron-emission tomography (FDG-PET), which detects active inflammation in the myocardium, resulted in increased detection of CS. A Heart Rhythm Society consensus statement in 2014 incorporated FDG-PET into its diagnostic criteria.[5] However, those criteria are not yet clinically validated, and data are particularly limited for the role of FDG-PET in guiding immunosuppressant titration.[6] The purpose of the present study was to report our experience using FDG-PET to diagnose CS and to guide therapies in patients with CS.

Methods

This was a retrospective single-center study in which we followed CS patients evaluated at Stanford University (Stanford, California) and managed based on our center's treatment protocol (Fig. 1) from March 2010 to August 2017. Methods of diagnosis are outlined in Table 1. Cardiac

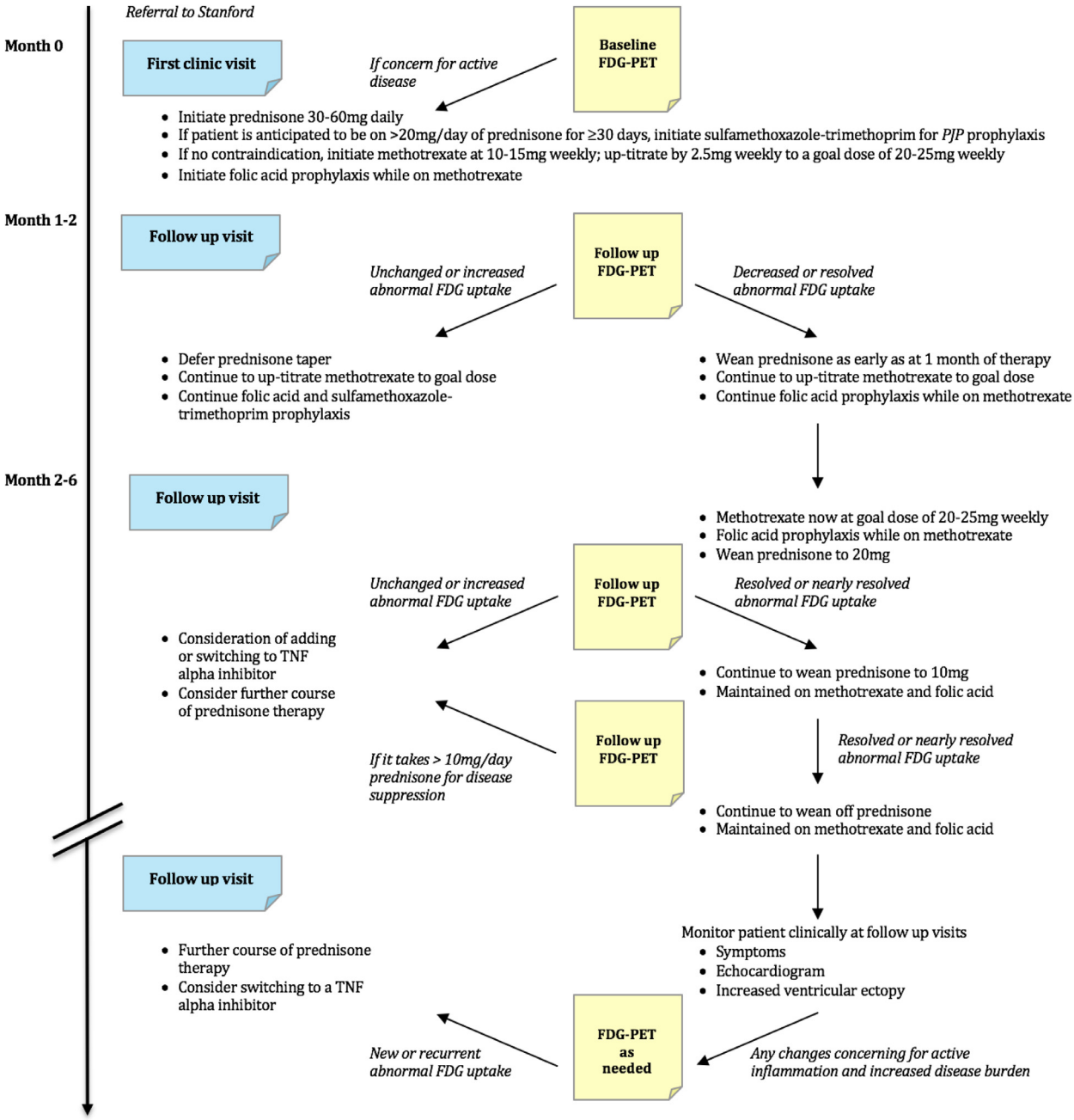

Fig. 1. Treatment protocol timeline for cardiac sarcoidosis. The goal is to wean prednisone to the lowest level possible with resolution or near-resolution of active disease. This protocol is applicable only if the patient has interpretable FDG-PET scans (ie, not scans with diffusely positive uptake). FDG-PET, fluorodeoxyglucose-positron emission tomography; PJP, *Pneumocystis jiroveci* pneumonia; TNF, tumor necrosis factor.

Table 1. Baseline Characteristics of Study Patients (n = 34)

Characteristic	Result
Age (y)	
Mean	61
Median (Q1−Q3)	59 (54−64)
Male sex	28 (82%)
Race	
White	25 (74%)
Black	5 (15%)
Hispanic	1 (3%)
Other (Asian, Pacific Islander, unknown)	3 (9%)
Method of diagnosis	
Positive* EMB	2 (6%)
Positive* noncardiac biopsy with cardiac symptoms† and imaging findings‡	15 (44%)
Clinical diagnosis with cardiac symptoms† and imaging findings‡	17 (50%)
EMB was attempted but negative	5 (15%)
FDG-PET was used for initial diagnosis of CS	21 (62%)
Initial cardiac presentation	
Heart block	16 (47%)
Heart failure	12 (35%)
Ventricular arrhythmias	14 (41%)
Extracardiac involvement (seen on FDG-PET imaging or via biopsy)	
Pulmonary	17 (50%)
Lymph nodes	18 (53%)
Liver	3 (9%)
Spleen	3 (9%)
Bone	2 (6%)
Other (renal, parotid gland, etc.)	3 (9%)
None (isolated CS)	10 (29%)
Baseline ejective fraction on transthoracic echocardiography	
Mean	51%
Median (Q1−Q3)	55% (41%−61%)
Baseline ejection fraction in patients who presented with heart failure	
Mean	36%
Median (Q1−Q3)	38% (32%−42%)
Baseline CMR available for 21 patients (62% of total patients)	
No LGE	4 (19%)
Positive LGE	17 (81%)
Cardiac catheterization available for 23 patients (68% of total patients)	
No CAD	17 (50%)
Minimal or nonobstructive CAD	5 (15%)
Obstructive CAD	1 (3%)
Not done or not available	11 (32%)

CAD, coronary artery disease; CMR, cardiac magnetic resonance; CS, cardiac sarcoidosis; EMB, endomyocardial biopsy; FDG-PET, fluorodeoxyglucose positron-emission tomography; LGE, late gadolinium enhancement.

*Positive biopsy defined as noncaseating granuloma characteristic of cardiac sarcoidosis.

†Including heart block, heart failure, and ventricular arrhythmias.

‡LGE on CMR or focal/patchy FDG uptake on FDG-PET.

manifestations included unexplained heart block, nonischemic cardiomyopathy, and ventricular arrhythmias. We excluded patients who did not undergo FDG-PET imaging. This study was approved by the Institutional Review Board. We collected data including age, sex, ethnicity, initial cardiac presentations, date and method of diagnosis, other organ involvement, transthoracic echocardiography (TTE), FDG-PET, cardiac magnetic resonance, and cardiac catheterizations. We recorded treatment changes, including rationale and whether FDG-PET contributed to the change. For outcomes, we examined the latest ejection fraction, PPM or ICD placement, hospitalizations, transplantation, and survival.

Patients were instructed to follow a noncarbohydrate diet for at least 12 hours before imaging to maximize suppression of physiologic myocardial glucose uptake.[7,8] Patients were scanned in 3-dimensional mode on a GE Discovery 600 PET/CT or a GE Discovery 690 PET/CT scanner (GE Healthcare, Milwaukee, Wisconsin). A cardiac computerized tomographic (CT) scan was performed spanning the entire heart (140 kV, 40 mAs, 512 matrix). After cardiac CT, cardiac PET was obtained for 12 minutes in 1 bed position over the heart. A whole-body PET/CT scan was also performed, with acquisition time of 3 minutes per bed position (47 slices/bed) in 6 beds with 11-slice overlap. PET emission scan was corrected with the use of attenuation data of the CT scan. PET images were reconstructed with the use of ordered subset expectation maximization with 2 iterations and 32 subsets for the GE Discovery 600 or 2 iterations and 24 subsets for the GE Discovery 690, following the manufacturer's recommendations. Each complete scan yields ∼12 mSV radiation exposure, which is similar to a noncontrast CT of the abdomen and pelvis. For reference, the average US background exposure is 3 mSV/y.

Continuous variables, such as age, ejection fraction, and medication dosage were summarized as mean ± SD. Dichotomous or ordinal variables were summarized as frequency and percentage of the total. Confidence intervals were calculated with the use of an alpha value of 0.05.

Results

See Table 1 for baseline characteristics.

FDG-PET Characteristics and Therapy Changes

A total of 128 FDG-PET scans were performed among 34 patients with a mean of 4 per patient. A mean of 3 scans were completed within the first year of follow-up. 59% of patients also underwent a baseline perfusion study at the time of their first FDG-PET scan. At baseline, 7 FDG-PET scans (21%) indicated no active cardiac sarcoid disease and 27 (79%) were abnormal. The most common patterns of abnormal FDG-uptake were patchy (n = 21) and patchy on diffuse (n = 4). Six patients (18%) had right ventricular involvement at baseline. Examples of uptake patterns are depicted in Supplemental Fig. 1. Among 128 scans, 94 (73%) contributed to a decision to change therapy (Table 2), defined as initiation, cessation, or switch of an immunosuppressant or a change in dosage. Forty-two scans (33%) contributed to the decision to taper prednisone. Five scans (4%) were of inadequate quality, potentially because of suboptimal dietary preparation.

Patient Outcomes

At median follow-up of 2.3 years, most patients received prednisone (n = 25; 74%) and methotrexate (n = 26; 76%). Nine (26%) were treated with TNF-α inhibitors after failing

Table 2. Serial FDG-PET and Decision Making in Therapy Management (n = 128)

Decision	n (%)
FDG-PET resulted in a change in therapy	94 (73%)
FDG-PET resulted in a decision to taper prednisone	42 (33%)
FDG-PET resulted in no change in therapy or not responsible for the change	32 (25%)
FDG-PET with poor preparation	5 (4%)
Within the first year*	
Total number of FDG-PET scans	85 (66%)
Mean FDG-PET scans per patient	3
Median FDG-PET scans per patient	2

FDG-PET, fluorodeoxyglucose positron-emission tomography.
*Defined as 1 year from the date of the initial FDG-PET scan.

adequate immunosuppression with the use of steroids and methotrexate or requiring an unacceptably high long-term maintenance dose (≥20 mg/d) of prednisone to achieve adequate ongoing suppression. Twenty-five patients (74%) received a PPM or ICD. Two patients (6%) underwent cardiac transplantation and were alive and well at the end of follow-up. Two patients (6%) died during follow-up; one death was without a known cause, and the other was attributed to urosepsis (Supplemental Table 1).

Discussion

CS management is evolving. To our knowledge, this is the first study to describe experiences and outcomes using FDG-PET to guide immunosuppressive therapy. We routinely incorporate serial cardiac FDG-PET in our management strategies. Over the past 7 years, we followed 34 patients who underwent 128 cardiac FDG-PET scans. FDG-PET aided in the initial diagnosis in more than half of our patient cohort and served as a valuable tool to assess response to therapy and to track disease burden. Three of every 4 scans contributed directly to a change in therapy. This finding is slightly higher but similar to the that of Ambrosini et al, where 22 of 35 scans (63%) influenced clinical management.[9]

Recent studies show high diagnostic potential for FDG-PET, with a sensitivity of 71%−100% and a specificity of 78%−90%.[10,11] Therefore, inclusion of FDG-PET may be more sensitive than established criteria.[12] Many centers are incorporating FDG-PET into their practice to aid diagnosis, but limited data exist on using FDG-PET to titrate therapy.[1−3,9,10,13,14]

Treatment Strategy

Our treatment approach is to initiate a steroid (eg, prednisone 30−60 mg/d) along with a steroid-sparing immunosuppressant (eg, methotrexate) for acute symptomatic management. Methotrexate is started at 10−15 mg/wk and up-titrated by 2.5 mg/wk every 2 weeks until a goal of 20−25 mg/wk is reached. We monitor blood counts, kidney function, and liver function tests at baseline and monthly during methotrexate up-titration and every 3 months thereafter. We assess patients in clinic every 1−2 months during active titration, with the first follow-up FDG-PET after 1−2 months to assess for therapy responsiveness. If a scan reveals resolved or near-resolved abnormal metabolic uptake, we begin steroid tapering as early as 1 month after initiation while continuing to up-titrate methotrexate to the goal dose. Subsequent scans are performed at prednisone doses of 20 mg, 10 mg, and 0 mg to assess for recurrence during tapering. If the scan is reassuring, we maintain patients on methotrexate alone. At that point, we perform additional scans only if there are signs or symptoms suggesting recrudescence of CS activity, with a goal of limiting lifetime radiation exposure. Figure 1 summarizes our treatment approach and algorithm. Supplemental Fig. 2 presents a sample patient's evolution of disease process and how FDG-PET scans are used to guide therapy.

Study Limitations

This manuscript represents the report of a single center's experience and does not have a control arm. However, despite the rarity and difficulty in recognizing and diagnosing this disease, our tertiary referral center provided a sizable cohort of CS patients. Although FDG-PET contributed greatly to our clinicians' decision to change therapies, we must recognize that they were not the only factor in decision making and they were not interpreted without the context of patients' clinical status, TTE, Holter monitoring, or ICD interrogations. Furthermore, although we limit the number of FDG-PET scans after the first 12 months, most patients received 3−4 scans over the course of the study; the potential long-term effects of radiation exposure cannot be assessed owing to the sample size and limited follow-up, although continued progress in FDG-PET dose reduction may enable lower radiation exposure in future cohorts.[15] Compared with reported natural histories for patients with CS, outcomes in our cohort were excellent, with 6% mortality at a median 2.3 years of follow-up. Half of our patients who were started on steroids initially were successfully weaned by 1 year. From our experience, FDG-PET allows for identification of patients who may require escalation of care for ongoing inflammation and allows for the identification of patients who may be able to tolerate more aggressive steroid tapering.

Conclusion

Our protocol of using serial FDG-PET scans for titration of immunosuppressive therapy with the near-universal addition of up-front steroid-sparing agents resulted in excellent outcomes compared with reported natural histories of patients with CS, with 6% mortality at a median 2.3 years of follow-up. Guided by FDG-PET imaging, half of the cohort who were initiated on steroids were able to be successfully weaned without evidence of active disease by 1 year of therapy.

Disclosures

None.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.cardfail.2019.02.018.

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