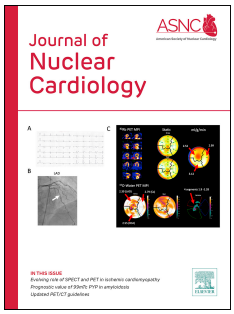

Serial ^{18}F-Fluorodeoxyglucose Positron Emission Tomography to Assess the Efficacy of Infliximab in Steroid Refractory Cardiac Sarcoidosis

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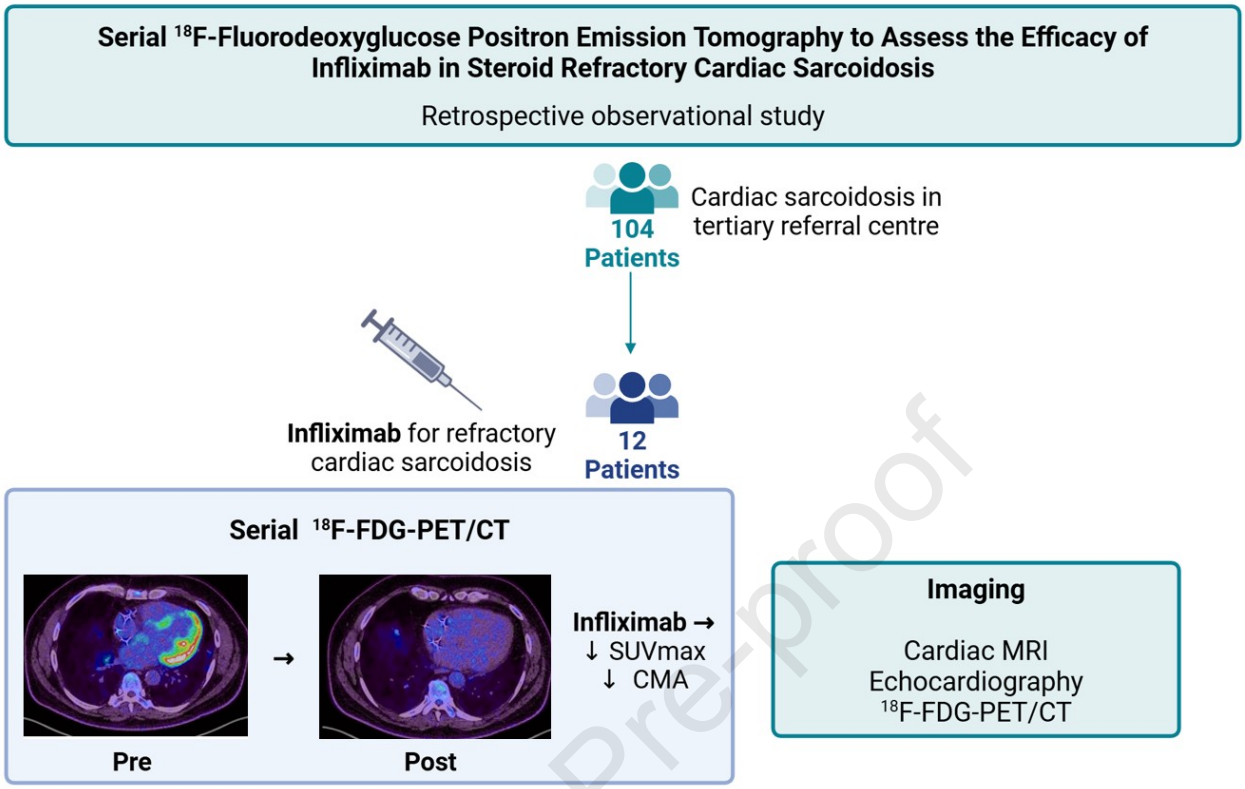

M Di Carli, MD, MASNC.
Brigham and Women's Hospital,
Boston, MA,
United States of America
23rd April 2025

Dear Editor,

Thank you for sending our manuscript entitled **"Serial 18F-Fluorodeoxyglucose Positron Emission Tomography to Assess the Efficacy of Infliximab in Steroid Refractory Cardiac Sarcoidosis"** out for review. We would like to thank you and the reviewers for their time and constructive comments, which we believe have helped us to significantly enhance the quality of the study manuscript.

Please find attached our revised manuscript below, both as a 'tracked' and 'clean' version to make it easy to see where we have made changes to the original version. We also attach a separate document containing detailed point-by-point responses to each of the reviewers' comments. Please note that the updated manuscript remains within the word limit outlined by the journal. However, in order to address some of the points raised by the reviewers we ask please for permission to include a total of eight rather than five references. We trust that you will now find it suitable for publication as a Research Letter in the Journal of Nuclear Cardiology.

Yours respectfully,

Dr William Moody, PhD, FACC, FESC.

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Serial ^{18}F-Fluorodeoxyglucose Positron Emission Tomography to Assess the Efficacy of Infliximab in Steroid Refractory Cardiac Sarcoidosis

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Conflicts of Interest: LEC, EJ, AR, TN, MY, and KH have no relevant conflicts of interest. AC has spoken in honorarium for Boehringer-Ingelheim and CSL Vifor. WEM has received advisory board fees from Alnylam, Astra Zeneca, Bayer, Bristol Myers-Squibb, Boehringer-Ingelheim, Pfizer, Sobi. This study has no relationship with industry and has no funding related to this study to disclose.

ABBREVIATIONS

ATP - Anti-tachycardia pacing

CMA - Cardiac metabolic activity

EF - Ejection fraction

^{18}F-FDG-PET/CT - Fluorodeoxyglucose-positron emission tomography/computed tomography

IQR - Interquartile range

LGE - Late gadolinium enhancement

LV - Left ventricular

MRI - Magnetic resonance imaging

RV - Right ventricular

SUV - Standardized uptake value

Introduction: Cardiac sarcoidosis is associated with high morbidity and mortality[1]. Management of cardiac sarcoidosis remains challenging with active myocardial inflammation and dysfunction requiring timely diagnosis and treatment. The lack of randomized clinical trials in cardiac sarcoidosis has led to treatment decisions being based on cohort studies and consensus opinions, with significant variation observed across centres. Corticosteroids are recommended as first line therapy despite a significant proportion of patients exhibiting inadequate treatment response. A small number of retrospective observational studies have reported that infliximab, an anti-tumor necrosis factor-alpha monoclonal antibody, may be effective in refractory cardiac sarcoidosis[2,3]. Based on expert consensus opinion, in 2023 National Health Service England recommended infliximab as an off-label routine commissioning treatment option for refractory sarcoidosis. We aimed to examine the efficacy of infliximab for the treatment of steroid refractory cardiac sarcoidosis using serial quantitative fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) imaging.

Methods: This retrospective observational cohort study was conducted at the Queen Elizabeth Hospital Birmingham, a World Association for Sarcoidosis and Other Granulomatous Disorders referral center for sarcoidosis in the United Kingdom. The study met local criteria for quality improvement activity and was approved by the University Hospitals Birmingham National Health Service Divisional Clinical Quality Group (Clinical Audit and Registration Management System-17020). Formal ethical approval was not required. Following review of hospital electronic health records, 12 out of 104 patients diagnosed with cardiac sarcoidosis between 01/11/2019 and 01/03/2024 (mean age: 55.2 +/- 11.4 years, 58% male) were identified as having received infliximab therapy for the management of refractory cardiac sarcoidosis and were included in this study. A high confidence diagnosis of cardiac sarcoidosis was made in accordance with Heart Rhythm

Society recommendations. All 12 patients had an extra-cardiac histological diagnosis of sarcoidosis alongside characteristic echocardiography, cardiac MRI (magnetic resonance imaging), and ^{18}F-FDG-PET/CT imaging. A strict dietary preparation protocol, as outlined by Manabe *et al*[5], was followed for all patients prior to ^{18}F-FDG-PET/CT imaging. Cases were discussed in a multidisciplinary meeting consisting of respiratory physicians, radiologists and cardiologists with expertise in imaging, heart failure and device therapy. Use of infliximab was limited to 'refractory disease' with ongoing cardiac inflammation as determined by ^{18}F-FDG-PET/CT, that had failed to respond within 6 months to 'standard treatment' which we defined as corticosteroids and/or at least one conventional disease modifying anti rheumatic drug such as methotrexate or azathioprine. The decision to initiate infliximab was always made at a multidisciplinary team level. This decision was primarily based on ^{18}F-FDG-PET/CT demonstration of persistence of myocardial maximum standardized uptake value (SUVmax) >2.5[4] but incorporated clinical as well as radiological findings. There was a lower threshold for initiating treatment with infliximab in those patients presenting with adverse clinical events in association with active cardiac disease (such as a requirement for inpatient admission for heart failure, reduction in left ventricular ejection fraction or life threatening arrhythmia including new atrioventricular block and/or ventricular arrhythmia).

Three initial induction doses of infliximab (5 mg/kg) were administered at week 0, week 2 and week 6. Subsequently, maintenance doses of infliximab were administered every 8 weeks for up to two years, discontinuing if there was no active inflammation evident on ^{18}F-FDG-PET/CT imaging. Treatment response was quantified by serial ^{18}F-FDG-PET/CT imaging. The clinical ^{18}F-FDG-PET/CT scan interpretation performed at the time of the exam acquisition was categorized as: 1) abnormal positive cardiac FDG uptake (focal or focal-on-diffuse), 2) negative FDG uptake, or 3) diffuse (non-specific) FDG uptake. Heterogeneity of FDG myocardial activity, a landmark of specificity of FDG for the diagnosis of cardiac

sarcoidosis, was assessed visually. Active myocardial inflammation was defined semi-quantitatively as a SUVmax ≥2.5[4]. Given the absence of a gold standard in cardiac sarcoidosis for quantifying myocardial uptake of FDG to assess therapeutic response, cardiac metabolic activity (CMA) was also assessed. CMA was calculated as metabolic accumulation volume (cm^3) x SUVmean, representing a composite parameter reflecting the total sarcoid myocardial burden[6].

Results: At baseline, seven (58%) patients had impaired left ventricular (LV) systolic function (defined as LV ejection fraction <50%) and ten patients (83%) had an implantable cardioverter-defibrillator device. Cardiac MRI data were as follows: LV ejection fraction 48% (IQR 36-69%), LV mass 155 ±46g, LV late gadolinium enhancement (LGE) present in 8 out of 12 (67%) patients, right ventricular (RV) ejection fraction 51±16%, and RV LGE present in 4 out of 12 (33%) patients. Baseline median values of high sensitivity Troponin I and NT-proBNP were 13 ng/L (IQR 12.3) and 388 ng/L (IQR 1510.5), respectively.

Infliximab was initiated at a median 4.0 years (IQR 8.8 years) after the patient's index presentation with sarcoidosis. After a median duration of infliximab therapy of 5 months (IQR 6 months), compared to baseline there were reductions in the LV SUVmax (13.3 (IQR 6.6) vs 5.1 (IQR 5.1), p=0.032), LV CMA (400 (IQR 485) vs 0 (IQR 170), p=0.002) and RV SUVmax (3.3 (IQR 2.5) vs 1.9 (IQR 0.8), p=0.074; Figure 1A-C. Ten patients had a reduction in CMA, with seven of these having a good response to infliximab based on a CMA reduction rate >70%, a marker of scintigraphic response and improved clinical outcomes in the PRESTIGE trial[6]. There were discordant findings between visual and semi-quantitative assessments: five out of the eleven (46%) initial follow-up ^{18}F-FDG-PET/CT studies supported focal active cardiac sarcoidosis (SUVmax ≥2.5) on semi-quantitative analysis despite being initially categorized as negative on visual assessment. In the 6 patients who have completed 2 years of infliximab therapy to-date, overall findings support a sustained

response as determined by the trend shown in ^{18}F-FDG-PET/CT imaging at baseline versus 2 years (baseline SUVmax 12.3 (IQR 9.2) vs 2 year SUVmax 3.9 (IQR 4.3), p=0.06). Representative serial ^{18}F-FDG-PET/CT images are displayed in Figure 1D-F, demonstrating complete and sustained metabolic remission in a typical patient, at baseline, 3 and 24 months after infliximab therapy. Of the 6 (50%) patients that reached 2 years duration of therapy, 4 (25%) were discontinued as per protocol after ^{18}F-FDG-PET/CT imaging demonstrated quiescent disease. Of those 4 patients, 1 had to be recommenced on infliximab after maintenance therapy with corticosteroids and a single conventional disease modifying anti rheumatic drug failed to suppress disease. Two patients remained on infliximab therapy beyond 2 years, one due to extra-cardiac indications and another due to ongoing myocardial inflammation.

There was no correlation between baseline hs-Troponin I and SUVmax (r_s=-0.09, p=0.81, Spearman's rank correlation coefficient) or CMA (r_s=-0.31, p=0.39, Spearman's rank correlation coefficient). Similarly, there was no correlation between baseline NTproBNP and SUVmax (r^2=0.02, p=0.75, Pearson correlation coefficients) or CMA (r^2=0.25, p=0.17, Pearson correlation coefficients). Due to the unavailability of follow-up cardiac biomarkers within this small cohort, we were unable to draw any meaningful correlations with scintigraphic responses to treatment.

With regards to tolerability of infliximab therapy, one patient reported a rash and one patient discontinued treatment after 2 months due to infection. The LV ejection fraction, assessed by echocardiography, remained stable following a median 11 months of infliximab treatment (pre-treatment LV ejection fraction: mean 38.6% (SD 17.6%) versus post-treatment LV ejection fraction: 46.6% (12.7%), p=0.263).

One patient required in-patient transfer for treatment of cardiogenic shock and suffered an arrhythmic sudden cardiac death on day 5 post-infliximab and therefore did not receive a

follow up ^{18}F-FDG-PET/CT. Only one patient on maintenance infliximab therapy experienced a single episode of ventricular tachycardia, which terminated with anti-tachycardia pacing. This patient's pre-infliximab ^{18}F-FDG-PET/CT imaging showed SUVmax 17.7, CMA 294 versus 5-month imaging demonstrating SUVmax 4.5, CMA 0. In the patient who discontinued infliximab at 2 months due to infection, the pre-treatment ^{18}F-FDG-PET/CT showed SUVmax 14.0, CMA 168 with follow-up imaging indicating SUVmax 3.7, CMA 0. This patient received 8 appropriate implantable cardioverter-defibrillator shocks for ventricular fibrillation and required ATP therapies to terminate multiple episodes of sustained ventricular tachycardia within the 2 year follow up period.

Discussion: This study is limited by its sample size, its retrospective single-center observational design and the non-randomized assignment of treatment. Furthermore, semi-quantitative analysis of heterogeneity (coefficient of variation) of myocardial FDG uptake, was not reported, which could have provided additional value[7,8]. Nonetheless, these data support that treatment with infliximab in patients with refractory cardiac sarcoidosis represents an effective strategy. Prospective trials are needed to fully inform the benefit of using infliximab in this condition.

New Knowledge Gain and Clinical Perspective:

1) What is new?
    - To-date, there are no published randomized controlled trials to guide treatment decisions on immunosuppressant therapy in CS. This real-world observational cohort study adds to the very limited evidence supporting the use of infliximab in patients with steroid-refractory disease.
2) What are the clinical implications?

- This study highlights the need to perform serial quantitative measures of FDG volume-intensity (cardiac metabolic activity, CMA), which may provide a more informative assessment of the response to immunosuppressive therapy than myocardial maximum standardized uptake value (SUVmax) or visual assessment *per se*.
- This study highlights a need for a prospective study to confirm the efficacy of infliximab therapy in the management of cardiac sarcoidosis; when designing such a trial, it will be important to include comparisons of visual and quantitative assessments of ^{18}F-FDG-PET/CT imaging that incorporate both SUVmax and CMA measurements.

DISCLOSURES: LEC, EJ, AR, TN, MY, and KH have no relevant conflicts of interest. AC has spoken in honorarium for Boehringer-Ingelheim and CSL Vifor. WEM has received advisory board fees from Alnylam, Astra Zeneca, Bayer, Bristol Myers-Squibb, Boehringer-Ingelheim, Pfizer, Sobi. This study has no relationship with industry and has no funding related to this study to disclose.

SOURCES OF FUNDING: None.

AUTHOR CONTRIBUTIONS

LEC, FL, AC and WEM designed the study. LEC, EJ, AR, TN, MY, KH collected and analyzed the dataset. All authors wrote, read and approved the research letter for submission.

DATA STATEMENT

The datasets are not publicly available and can solely be accessed by the authors.

ETHICS

The study met local criteria for quality improvement activity and was approved by the University Hospitals Birmingham NHS Divisional Clinical Quality Group (Clinical Audit and Registration Management System-17020). Formal ethical approval was not required.

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FIGURES AND LEGENDS

Graphical abstract

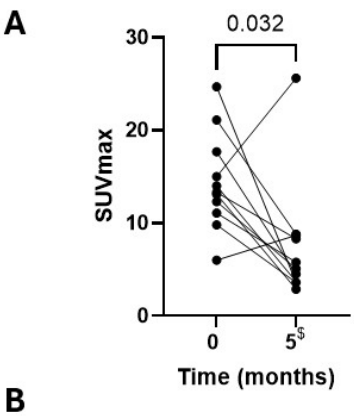
Legend: Graphical abstract summarizing the findings of this observational study, which through serial ^{18}F-FDG-PET/CT imaging, supports the use of infliximab in the management of refractory cardiac sarcoidosis**.** CMA - cardiac metabolic activity, EF - ejection fraction, ^{18}F-FDG-PET/CT - fluorodeoxyglucose-positron emission tomography/computed tomography, LV - left ventricular, MRI - magnetic resonance imaging, SUV - standardized uptake value

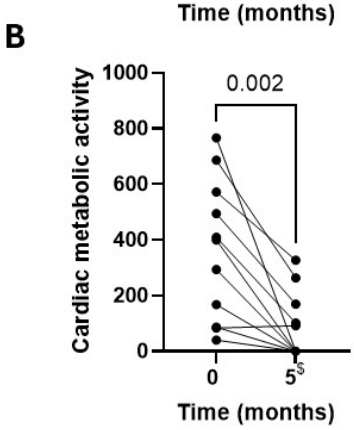
Figure 1: ^{18}F-FDG-PET/CT imaging demonstrates treatment response to infliximab in cardiac sarcoidosis.

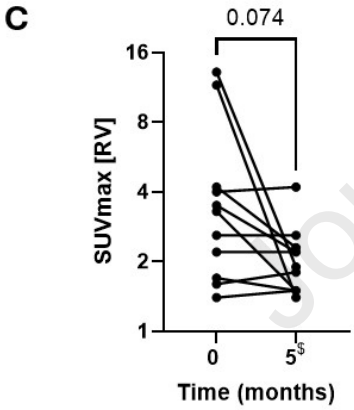
(A, B and C) Serial ^{18}F-FDG-PET/CT findings in patients with steroid refractory cardiac sarcoidosis treated with infliximab. $^{\$}$Follow-up ^{18}F-FDG-PET/CT imaging performed at a median 5 months (IQR 6 months) after starting infliximab. Changes in **(A)** LV maximal metabolic disease activity (SUVmax), **(B)** LV total disease activity (cardiac metabolic activity, CMA) and **(C)** RV maximal metabolic disease activity (SUVmax [RV]) following infliximab. Wilcoxon tests performed. One patient is presented twice as two courses of infliximab were administered over 4 years due to disease relapse within 3 months of suspending infliximab at 2 years.

(D, E and F) Serial ^{18}F-FDG-PET/CT imaging in a patient presenting with exertional dyspnea and subsequent symptomatic high-grade atrioventricular block, and impaired LV systolic function.

(D) Baseline imaging in patient with steroid refractory sarcoidosis. **(E)** Imaging at 3 months demonstrates complete metabolic resolution in all LV regions. **(F)** Imaging at 2 years following continued infliximab therapy demonstrates continued complete metabolic remission. CMA - cardiac metabolic activity, ^{18}F-FDG-PET/CT - fluorodeoxyglucose–positron emission tomography/computed tomography, LV - left ventricular, LVEF - LV ejection fraction, RV - right ventricular, SUVmax – maximum standardized uptake value.







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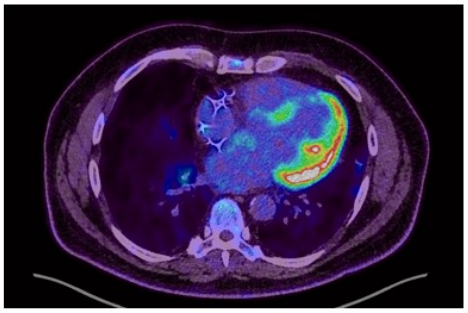
^{18}F-FDG-PET/CT



SUVmax 13.1 | CMA 767

Infliximab commenced

E: 3-months post
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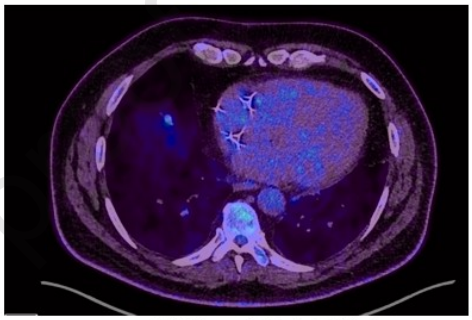
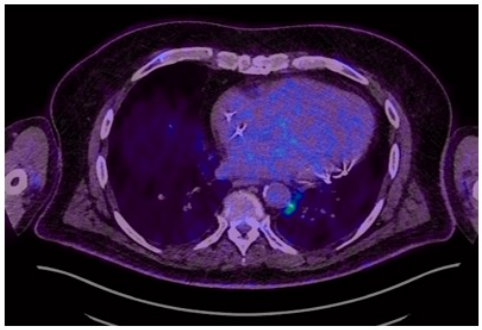


SUVmax 2.9 | CMA 0

Infliximab continued

F: 24-months post
^{18}F-FDG-PET/CT



SUVmax 3.9 | CMA 0

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Anjali Crawshaw reports a relationship with Boehringer-Ingelheim that includes: speaking and lecture fees. Anjali Crawshaw reports a relationship with CSL Vifor that includes: speaking and lecture fees. William E. Moody reports a relationship with Alnylam that includes: consulting or advisory. William E. Moody reports a relationship with AstraZeneca that includes: consulting or advisory. William E. Moody reports a relationship with Bayer that includes: consulting or advisory. William E. Moody reports a relationship with Bristol Myers-Squibb that includes: consulting or advisory. William E. Moody reports a relationship with Boehringer Ingelheim that includes: consulting or advisory. William E. Moody reports a relationship with Pfizer that includes: consulting or advisory. William E. Moody reports a relationship with Sobi that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.