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Role of serial F-18 FDG PET/CT scans in assessing treatment response and predicting relapses in patients with symptomatic sarcoidosis

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Abstract. *Background:* Monitoring disease activity in sarcoidosis remains a clinical challenge as there is no gold standard. Positron emission tomography (PET) imaging is a novel tool to assess the metabolic activity. There is limited data on the role of serial PET scans in monitoring the disease activity. *Methods:* This is a prospective study of 27 sarcoidosis patients treated with systemic corticosteroids. Patients underwent two serial PET/CT scans: one before initiating therapy and the follow up scan at end of therapy. The metabolic response on PET scan was classified as: (a) complete metabolic response (CMR); (b) partial metabolic response (PMR); (c) stable metabolic disease (SMD); and, (d) progressive metabolic disease (PMD). Patients with either CMR or PMR were classified as PET responders while those with SMD or PMD were considered as PET non-responders. All patients were followed at 3, 6 and 12 months after completion of therapy. Relapse rates and relapse-free survival was compared between the various groups. *Results:* There was significant decline in the median SUVmax of the mediastinal lymph nodes, peripheral lymph nodes and the lung parenchyma in the follow up PET scan. Eight patients achieved CMR, 6 patients achieved PMR while 13 patients were PET non-responders. There was no difference in the clinical remission rates between the responders and non-responders. However, the relapse rate was significantly higher in non-responders vs. responders (61.5% vs. 14.2%, p=0.018). None of the patients who achieved a CMR relapsed during the study period. *Conclusions:* Patients with metabolic response on PET scan have significantly fewer relapses as compared to those with no response on PET scan. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 372-380)*

Key words: sarcoidosis, response assessment, positron emission tomography, metabolic activity, predicting relapse

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. The clinical presentation is variable and can range from an asymptomatic incidentally detected disease to a fulminant life-threatening illness. The clinical course is also variable ranging from a self-remitting illness to a chronic relapsing disease. The therapy for sarcoidosis depends on the organs involved, the clinical symptoms and the functional limitation produced. Corticosteroids

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are the most commonly used agents for the initial treatment of sarcoidosis (1). Though most patients with pulmonary and other forms of sarcoidosis respond to treatment initially, a significant proportion experience a relapse once the therapy is discontinued,(2) with most relapses occurring within one year of discontinuing therapy.

The assessment of disease activity in sarcoidosis remains problematic as there exists no gold standard. Treatment decisions in pulmonary sarcoidosis are based on combined assessment of clinical symptoms, radiographic images and pulmonary function tests. F-18 fluoro-deoxy-glucose (FDG) positron emission tomography (PET) imaging has emerged as a novel tool for imaging the inflammatory activity in sarcoidosis. Combining FDG PET and computed tomography (CT) imaging has an added advantage of simultaneously assessing the anatomic and the functional extent of the disease. Several studies have assessed the role of FDG PET scans in assessing the disease activity.(3) FDG PET imaging has been shown to be superior to gallium 67 (Ga-67) scans (4). FDG PET has also been shown to be more sensitive in evaluating disease activity compared to other serum inflammatory markers like angiotensin converting enzyme (ACE), neopterin and the soluble interleukin 2 receptor (sIL2R) (5-7). The presence of FDG avid pulmonary parenchyma has been shown to predict future decline in lung function if left untreated (8). Increased SUVmax (>6) and a higher retention index at the baseline have been shown to predict future relapses and persistent pulmonary disease, respectively (9, 10).

Few studies however, have assessed the role of serial PET scans in monitoring disease activity in sarcoidosis. Early metabolic response on PET scan within 1-2 months of initiating corticosteroids has been noted (11, 12). However, the response on PET scan is not always uniform and some patients continue to have persistent metabolic activity after therapy (13, 14). The clinical significance of metabolic response on PET scan has not been studied in larger samples. Also, there is limited data on the ability of PET scan to predict future relapses (10).

We have recently reported the performance of FDG PET/CT scans in differentiating sarcoidosis from tuberculosis (15). Herein, we present the results of follow up PET-CT scans in patients with sarcoidosis. In this study, we assessed (a) change in metabolic activity after therapy with systemic corticosteroids; (b) correlation of the metabolic response on serial PET imaging with the patients' clinicoradiologic response; and, (c) the ability of a metabolic response on PET imaging to predict future relapses.

Methods

This prospective study included treatment naïve symptomatic sarcoidosis patients who underwent a baseline 18-F FDG PET/CT scan between July 2012 and June 2013. The baseline 18-F FDG PET/CT findings in patients with sarcoidosis have already been published (15). Briefly, the inclusion criteria were the presence of mediastinal lymphadenopathy with a clinicoradiologic suspicion of sarcoidosis. The exclusion criteria were uncontrolled diabetes mellitus (fasting plasma glucose >150 mg/dL), renal failure (serum creatinine >2 mg/dL), uncorrected coagulopathy, history of contrast allergy or contrast nephropathy, hypoxia on room air (arterial oxygen saturation <90%), severely deranged lung function (forced vital capacity or forced expiratory volume in the first second < 50% of predicted), pregnancy and lactation. A diagnosis of sarcoidosis required a clinicoradiologic picture consistent with sarcoidosis and/or demonstration of granulomas on lung biopsy or lymph nodal aspirates and clinicoradiologic improvement with the use of corticosteroids. The patients were treated with tapering doses of corticosteroids for a minimum duration of six months and a repeat PET scan was performed at the end of the treatment period. Patients who were not treated with corticosteroids and those who did not undergo a follow-up PET scan were also excluded from the current analysis.

Preliminary laboratory investigations included tuberculin skin test (TST), serum angiotensin converting enzyme (ACE) levels, renal function tests, calcium profile, complete blood count, coagulation profile and spirometry.

18-F FDG PET/CT image acquisition and analysis

All patients underwent a whole body PET/CT scan using a hybrid scanner (Discovery STE-16, GE Healthcare, Milwaukee, USA), 60 minutes after intravenous injection of 370-444 MBq of F-18 FDG as per the procedure described earlier (15). The fol-

low up PET/CT was performed in a similar manner as the first scan in terms of the FDG dose given, injection to image acquisition time, data acquisition, reconstruction and image analysis.

Image analysis

The FDG PET/CT scan findings were considered positive if FDG uptake was more than the blood vessels in the mediastinum (mediastinal blood pool) Increased uptake in extrathoracic sites, including lymph nodes, musculoskeletal system and visceral organs like liver or spleen was taken as positive. For quantitative analysis of FDG uptake, a 9x9 mm region of interest (ROI) was carefully drawn on consecutive 4-6 PET slices. The ROI showing the maximum SUV out of these PET slices was taken as SUVmax.

All images were reviewed jointly by two nuclear medicine physicians. SUVmax, a semi-quantitative parameter was calculated. The mean SUVmax for the lymph nodal stations in the mediastinum was also calculated (SUVaverage or SUVavg).

Metabolic response assessment

The metabolic response on the follow up PET scans was assessed separately for each site of involvement (mediastinal nodes, peripheral nodes, abdominal nodes and the lung parenchyma). The metabolic response was either based on SUVavg (for the mediastinum) or the SUVmax (for lung parenchyma and the extrapulmonary organs). The metabolic response was classified into four groups:

(a) Complete metabolic response (CMR): decrease in SUVavg/SUVmax of >75% from baseline
(b) Partial metabolic response (PMR): decrease in the SUVavg/SUVmax between 25% and 75%
(c) Stable metabolic disease (SMD): decrease in SUVavg/SUVmax <25% or an increase in SUVavg/SUVmax ≤25%
(d) Progressive metabolic disease (PMD): increase in the SUVavg/SUVmax more than 25%.

An overall PET response was then assigned to each patient based on the response pattern at various sites. For patients who had different metabolic response patterns at different sites, a consensus meeting was held to decide on the final categorization of the response. In general, an increase in metabolic activity at any site was classified as lack of response. The patients were then classified into two broad groups: PET responders and PET non-responders. Patients with either a CMR or a PMR were classified as PET responders. Those with SMD and PMD were classified as PET non-responders.

Clinicoradiologic response assessment and follow up

During the course of treatment, patients were followed up at three monthly intervals. A detailed assessment of the symptoms was done at each visit and a chest radiograph was also obtained. A patient was considered to be in remission if there was resolution of clinical symptoms (>75% reduction in subjective perception of the intensity of symptoms) as well as significant improvement in the chest radiographs. Therapy was stopped in such patients. Those with persistent symptoms needing corticosteroids or steroid sparing agents were considered not to be in remission. The decision to stop corticosteroids was made on clinical grounds alone and the findings of the follow up PET scan were not taken into consideration. All the patients were then followed up at three, six and twelve months and assessed for disease relapse. Clinical and radiologic details were noted. A relapse was defined as worsening of clinical symptoms (pulmonary or extrapulmonary) and/or a radiologic progression with no other alternative cause identified and necessitating reintroduction of steroids/steroid sparing agents. Patients were considered to have a sarcoid relapse only if their symptoms responded to reinstitution of steroids/steroid sparing agents.

Statistical analysis

Data was tabulated and analysed using the statistical package SPSS (ver 22.0, SPSS Inc., USA). The baseline parameters between the two groups were compared using either the chi-square or the Mann Whitney U test. The baseline and follow up PET scan imaging findings were compared using the Wilcoxon matched pair signed rank test. The disease remission rates and the relapse rates between the various groups were compared using either the chi

square or the Fishers exact test. The relapse free survival between the various groups was compared using the Kaplan Meier survival curves.

Results

Of the 88 patients who underwent a baseline PET scan, treatment with corticosteroids was instituted in 79 patients. A follow up PET scan was performed in 27 patients and these have been included in the present study. The demographic and clinical parameters are shown in Table 1. In 25 patients, the diagnosis of sarcoidosis was established by histo/cytopathologic demonstration of granulomas [transbronchial lung biopsy (n=18), endobronchial biopsy (n=12), transbronchial needle aspiration (n=14), liver biopsy (n=1), skin biopsy (n=1) and orbital biopsy (n=1)], and clinical response to oral corticosteroids. In two patients, granulomas could not be demonstrated and diagnosis was made on suggestive clinicoradiologic picture and response to oral corticosteroids. The most common indication for corticosteroids was symptoms of cough and dyspnea (n=15). The mean

Table 1. Demographic and clinical characteristics of the study population

	PET responders (n=14)	PET non responders (n=13)	Overall (n=27)	P value
Age (years)	43.3±10.9	51.0±9.4	47±10.7	0.557
Male gender	6 (42.9)	4 (33.3)	10 (37)	0.695
Clinical presentation				0.580
Pulmonary	6 (42.9)	6 (46.2)	12 (44.4)	
Extrapulmonary	6 (42.9)	3 (23.1)	9 (33.3)	
Both	1 (7.1)	3 (23.1)	4 (14.8)	
Constitutional only	1 (7.1)	1 (7.7)	2 (6.4)	
Symptoms and signs				
Cough	7 (50)	9 (69.2)	16 (59.2)	0.551
Dyspnea	2 (14.3)	5 (38.5)	7 (25.9)	0.209
Wheeze	0	1 (7.7)	1 (3.7)	0.481
Fever	5 (35.7)	3 (23.1)	8 (29.6)	0.678
Anorexia	4 (28.6)	4 (30.8)	8 (29.6)	1.000
Weight loss	5 (35.7)	3 (23.1)	8 (29.6)	0.678
Palpable lymphadenopathy	2 (14.3)	0	2 (7.4)	0.481
Hepatosplenomegaly	2 (14.3)	0	2 (7.4)	0.481
Extrapulmonary involvement				
Eyes	4 (28.6)	3 (23.1)	7 (25.9)	0.681
Skin	2 (14.3)	4 (30.8)	6 (22.2)	0.385
Joints	5 (35.7)	3 (23.1)	2 (7.4)	0.678
Hepatic	2 (14.3)	0	1 (3.7)	0.481
Neurologic	1 (7.1)	0	8 929.6)	1.000
Sarcoidosis health questionnaire				
Daily functioning	5.0±0.9	5.0±1.0	5.0±0.93	0.799
Physical functioning	5.2±0.8	5.4±0.5	5.3±0.7	0.237
Emotional functioning	5.0±0.6	4.8±1.0	4.9±0.9	0.311
Total score	5.1±0.6	5.1±0.6	5.1±0.6	0.792
Serum calcium, mg/dL	9.2±0.6	9.1±0.6	9.1±0.6	0.790
Serum ESR, mm/hr	37.4±20.5	36±27.3	36.7±23.4	0.398
Elevated serum ACE level	10 (71.4)	7 (53.8)	17 (62.9)	0.965
Pulmonary function testing				
FVC, litres	3.2±1.1	2.9±0.9	2.99±0.9	0.529
FVC, %predicted	101.5±14.1	95.3±21.2	97.9±18.4	0.337
Chest radiograph				0.648
Scadding stage 1	12 (85.7)	10 (76.9)	22 (81.5)	
Scadding stage 2	2 (14.3)	3 (23.1)	5 (18.5)	
Chest CT scan				
Parenchymal nodules	10 (71.4)	10 (76.9)	20 (74.1)	1.000
Consolidation	3 (21.4)	2 (15.4)	5 (18.5)	1.000
Ground glass opacity	2 (14.3)	5 (38.5)	7 (25.9)	0.209

Data are presented as mean ± S.D. or number (percentage)
ACE: angiotensin converting enzyme; CT: computed tomography; ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; PET: positron emission tomography

(±SD) duration of corticosteroid therapy was 9 (± 3) months. All the patients had symptomatic improvement after initiation of corticosteroids.

Metabolic response

Of the 27 patients, 14 (51.9%) had a favourable metabolic response on PET scan (PET responders: CMR- eight patients, PMR- six patients) and 13 (48.1%) patients had no metabolic response on PET scan (PET non responders: SMD- six patients, PMD- seven patients). The baseline clinical and demographic characteristics were similar between these two groups (Table 1). Also, the baseline PET characteristics were not different between the two groups (Table 2).

Quantitative analysis of the SUVmax per focus was done for initial and follow up scans and the metabolic response were assessed (Tables 3 and 4). There was significant decrease in the median SUVmax of the mediastinal nodes in the follow up scan (12.6 vs 5.8, p=0.002). Similarly, there was a signifi-

Table 2. Baseline FDG uptake patterns and the intensity of uptake

	PET responders (n=14)	PET non responders (n=13)	Overall (n=27)	P value
Lymph nodal FDG uptake				
Mediastinal	14 (100)	13 (100)	27 (100)	-
Abdominal	12 (85.7)	8 (61.5)	20 (74)	0.209
Peripheral	10 (71.4)	12 (92.3)	22 (81.5)	0.326
Pulmonary parenchymal FDG uptake	11 (78.5)	11 (84.6)	22 (81.5)	1.000
Extra-pulmonary FDG uptake				
Any	7 (50)	5 (38.5)	12 (44.4)	0.704
Liver	4 (28.5)	1 (7.7)	5 (18.5)	0.326
Spleen	1 (7.1)	2 (15.4)	3 (11.1)	0.596
Orbit	1 (7.1)	0	1 (3.7)	1.000
Salivary glands	2 (14.3)	2 (15.4)	4 (14.8)	1.000
Thyroid	1 (14.3)	2 (15.4)	3 (11.1)	0.596
Musculoskeletal	1 (7.1)	1 (7.7)	2 (7.4)	1.000
Intensity of FDG uptake				
SUVmax	14.4 (10.9-18.6)	8.7 (6.0-16.4)	12.6 (8.2-18.5)	0.085

Data are expressed as number (percentage) or median (interquartile range).
PET: positron emission tomography; FDG: fluoro deoxy glucose; SUV: standardized uptake value

Table 3. Comparison of the baseline and follow up PET scan SUV values

	Initial PET scan	Follow up PET scan	P value
Mediastinum nodes			
SUVmax	12.6 (8.2-18.5)	5.8 (2.4-14.0)	0.002
SUVavg	10.4 (6.3-12.7)	3.6 (0.8-8.8)	0.003
Peripheral nodes	4.7 (2.5-8.6)	0 (0-5.0)	0.033
Abdominal nodes	7.9 (3.1-11.3)	1.6 (0-8.3)	0.100
Lung parenchyma	6.1 (4.6-9.5)	0 (0-4.3)	0.002
Extrathoracic organs	6.7 (4.9-10.5)	5.1 (0.6-10.2)	0.182

Data are expressed as median (Interquartile range)

Table 4. Metabolic response to steroid therapy (stratified according to site)

	Mediastinal nodes (n=27)	Peripheral nodes (n=22)	Abdominal nodes (n=23)	Lung parenchyma (n=23)
Complete metabolic response	5 (18.5)	13 (59.9)	11 (47.8)	11 (47.8)
Partial metabolic response	11 (40.7)	2 (9.1)	3 (13)	3 (13)
Stable metabolic disease	6 (22.2)	3 (13.6)	4 (17.4)	6 (26.1)
Progressive metabolic disease	5 (18.5)	4 (18.2)	5 (21.7)	3 (13)

Data are expressed as number (percentage)

cant decrease in the median SUVmax for the lung parenchyma and the peripheral nodes. However, the decrease in SUVmax for the abdominal nodes and the extrapulmonary organs was not statistically significant. On the follow up PET scan, a favourable metabolic response (CMR or PMR) was seen in 59.2%, 69%, 60.8% and 60.8% of the patients at mediastinal nodes, peripheral nodes, abdominal nodes and the lung parenchyma, respectively.

Clinicoradiologic response

Based on the clinicoradiologic assessment done at the time of follow up PET scan, all except two patients were in clinical remission. In these two patients who had relapsed while on steroid taper, the steroid dose was hiked and oral methotrexate was added. Treatment was stopped in the remaining patients and they were then followed up and assessed for disease relapse.

Correlation of metabolic response with clinical outcomes

Of the 25 patients who were in clinical remission, 56% had a metabolic response on PET scan, either a CMR or PMR, whereas 44% had no metabolic response on PET scan. The two patients who were not in clinical remission at the time of follow up PET scan did not have a metabolic response on PET scan. The correlation between the clinicoradiologic response and the metabolic response in our study was poor (κ=0.16, p=0.127).

Table 5. Clinical remission and relapse rates of the study population

	PET responders (n=14)	PET non responders (n=13)	P value
Clinical remission at the time of follow up PET scan	14 (100)	11 (83.3)	0.222
Relapse rates			
3 months	1 (7.1)	4 (30.8)	0.165
6 months	1 (7.1)	5 (38.5)	0.077
12 months	2 (14.2)	8 (61.5)	0.018

Data are presented as number (percentages)

Follow up and relapse assessment

The median duration of follow up was 341 days (interquartile range: 267-390 days). The relapse rates at 3, 6 and 12 months are shown in Table 5. None of the eight patients who had a complete metabolic response on PET scan relapsed during the follow up period. When the relapse rate of this subgroup was compared with those who did not achieve a CMR, the difference was statistically significant (0/7 vs. 10/20, p=0.027) (Figure 1a). Similarly, a higher

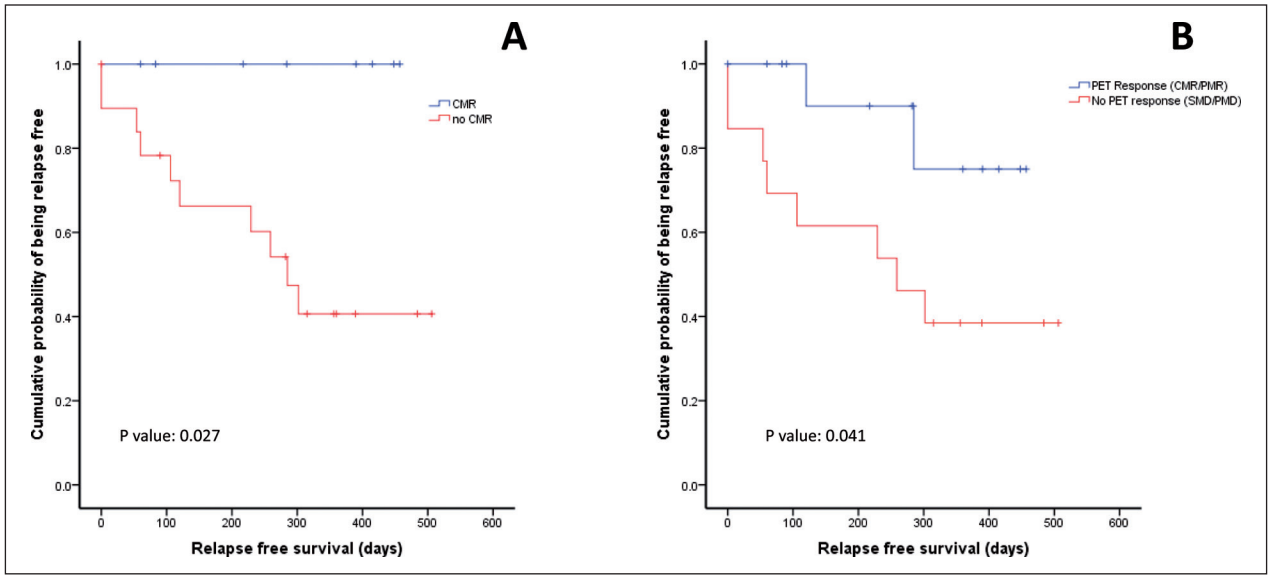

Fig. 1. Kaplan Meier curves for relapse free survival compared between the patients with a complete metabolic response (CMR) and those without a CMR. **b**: Kaplan Meier curves for relapse free survival compared between the patients with a response on PET scan (CMR or PMR) and those without a response on PET scan (SMD or PMD)

percentage of patients (61.5%) with no response on PET scan (SMD or PMD) relapsed by 12 months as compared to those with a response on PET scan (CMR or PMR). Kaplan- Meier curves were used to compare the relapse free survival between these two groups (Figure 1b).The difference between the two groups was significantly different (p=0.041).

Discussion

The results of this study suggest that metabolic response on follow up PET scan can predict the future risk of relapses but does not correlate with the resolution of clinical symptoms. The disease activity in sarcoidosis is traditionally assessed and monitored by the clinical symptoms, chest radiographs and pulmonary function tests (PFT). However, these modalities are far from being perfect, and hence many other candidate markers have been tested. These include serum ACE levels, sIL2R levels, serum neopterin levels, bronchoalveolar lavage lymphocyte percentage, high resolution computed tomography scan and the Ga-67 scan. None of these have been shown to contribute significantly to the information obtained by conventional chest radiographs and PFTs (16). FDG PET/CT scan is a novel imaging modality, which not only detects the anatomic extent of the disease but also the metabolic activity.

The results of the current study suggest that the metabolic response on PET scan following oral corticosteroids is variable among patients. In fact, only 14 (51.9%) patients had PET response, either complete or partial, and seven (25.9%) patients had progressive disease. Similar variability in response has been noted in earlier studies. In the study by Tierstein at al. a follow up PET was done after three months of corticosteroids and a decrease in SUV was noted in only 11 of the 51 patients (21.6%) (17). In another study, 30 patients underwent a follow up PET scan after one year of treatment with corticosteroids and methotrexate. There was a PET response in 21 patients (70%) and progressive disease on PET in nine patients (30%) (14). There was however a 92% PET response (11/12 patients) after six months therapy with infliximab.(18) This difference in response on PET between various studies can be attributed to the different drugs used and the varying durations of treatment.

The decrease in inflammatory activity (SUVmax) on PET scan was also not uniform across the various sites of active disease. A significant decrease in the SUVmax was seen in the mediastinal nodes, lung parenchyma and the peripheral nodes but not in other locations. In our study, SUVavg was used for mediastinal lymph nodes as several lymph nodes stations were involved whereas for other sites SUVmax was used due to involvement of one or two sites only. These results are consistent with earlier published reports, which also have noted similar pattern of decrease.(14) As the baseline clinical, demographic and baseline PET characteristics were similar between PET responders and non-responders, it is not possible to predict patients who are likely to have a metabolic response on PET scan.

Several studies have assessed the role of serial PET scans in monitoring disease activity (Table 6) (13, 14, 17, 18). The results of our study show that the clinical remission rates were similar for patients with and without response on PET scan (100% vs 83.3%, p=0.22). A recent study on 25 patients correlated the metabolic response on PET scan with the clinical and the radiologic response. They showed that the correlation between the metabolic response and the clinical response is only moderate (κ=0.44) whereas the correlation between the radiologic and the metabolic response was better (κ=0.70).(19) The disparity in results between the current and the previous studies is likely due to several factors: (a) different clinical characteristics of the included patients (treatment naïve patients vs. pretreated patients); (b) different drugs used and differing durations of treatment; (c) differences in the method of assessing metabolic response on PET scan (single point SUVmax vs. a global assessment of the disease activity); (d) differences in the categorization of the clinical and metabolic response (two vs. three groups); and, (e) differences in the radiologic modality used to assess the response (chest radiograph vs. CT chest). Future studies should employ uniform criteria for clinicoradiologic and metabolic response assessment to determine the accuracy of PET scan in assessing treatment response.

None of the eight patients who achieved a complete metabolic response on PET scan relapsed during the 12 months follow up. On the contrary, two of the six patients (33.3%) with a partial metabolic response and 8 of the 13 patients (61.5%) with no response on PET scan had a relapse. Thus, serial assess-

Table 6. Comparison of the studies which compared metabolic response on PET scan with clinicoradiologic outcomes

	Braun, et al (2008) (13)	Keijsers, et al (2008) (18)	Saranovic, et al (2013) (14)	Guleria, et al (2014) (19)	Current study
No. of patients with two serial PET/CT scans	5	12	30	21	27
Basis for diagnosis of sarcoidosis	Biopsy proven sarcoidosis	Biopsy proven sarcoidosis	Biopsy proven sarcoidosis	ATS/ERS/WASOG criteria 1999	Biopsy proven sarcoidosis
Inclusion criteria	Treatment naïve and symptomatic	Resistant/intolerant to conventional therapy with steroids	Patients who are on/post treatment and have persistent symptoms	Treatment naïve and symptomatic	Treatment naïve and symptomatic
Treatment received	Varying duration of steroid treatment (2,6,16,19 and 21 months)	6 months treatment with Infliximab	At least 6 months of treatment with steroids ± methotrexate (mean treatment duration 12 ± 5 months)	6-9 months of steroid therapy	6-12 months of steroid therapy
Clinical response assessment	Not mentioned	Categorized as -Improved -No change	Patients perception of symptoms -Improved -Same as before -Worsened	Complete: Disappearance of all symptoms. Partial: Persistence of one or more symptoms No response: Worsening of one or more symptoms	Patients perception of symptoms -Remission (<75% reduction from baseline) -Not in remission
Radiologic response assessment	Not mentioned	CXR used for follow up. No objective criteria.	Not done	HRCT used for follow up assessment. Objective criteria used. Categorized as -Complete -Incomplete -No response	CXR used for follow up. No objective criteria.
PET response assessment criteria	All sites of uptake assessed individually. No cutoffs used	All sites assessed visually. Maximum change in single point SUVmax (%) used. No categorization of response	Classified based on visual assessment and a single point SUVmax value Improved/Same Worsened	Used a single point SUVmax to assess metabolic response. Complete: >70% decrease Partial: 20-70% decrease No response: <20% decrease	Global assessment of PET scan. Response at each site of uptake assessed individually. -CMR: >75% decrease -PMR: 25-75% decrease -SMD: -25% to +25% decrease -PMD: >25% increase
Patients with a metabolic response on PET scan, n/N (%)	2/5 (40%)	11/12 (92%)	21/30 (70%)	17/21 (80.9%)	14/27 (51%)
Patients with clinical improvement but no response on PET scan, n/N (%)	0/2	0/10	5/25 (20%)	3/9 (33%) Exact numbers not mentioned for patients with partial response of symptoms	11/25 (44%)
Patients with no clinical improvement but response on PET scan, n/N (%)	0/3	0/2	1/5 (20%)	0/1	0/2

ATS: American thoracic society; CMR: complete metabolic response; CT: computed tomography; CXR: chest radiograph; ERS: European respiratory society; PET: positron emission tomography; PMD: progressive metabolic disease; PMR: partial metabolic response; SMD: stable metabolic disease; WASOG: World association for sarcoidosis and other granulomatous disorders.

ment of metabolic activity on PET scans might help in the prediction of future relapses. To the best of our knowledge, this is the first study in which metabolic response on PET scan performed at the completion of therapy was correlated with the risk of future relapses. The results of this study are hypothesis-generating. Titrating therapy to achieve a metabolic response might be used as an end point for therapy in sarcoidosis. However, further research is required in assessing superiority of such PET response (achieving a CMR or a PMR) guided therapy compared to conventional clinicoradiologic criteria based therapy.

There are a few limitations to the current study. Firstly, the sample size is limited. The study results need to be validated by larger prospective study. Secondly, there are no consensus criteria for assessing the metabolic response on PET scan in sarcoidosis. Though PERSIST 1.0 criteria(20) and EORTC criteria (21) have been proposed, these are primarily intended for solid tumors and lymphomas. We have used arbitrary cut offs for assessing treatment response in the current study. Standardization of response criteria for PET scan in sarcoidosis is needed.

Conclusions

A metabolic response on a PET scan performed at completion of therapy can predict the future risk of relapses but does not correlate with the clinical response of the patient. Patients with a complete metabolic response do not have future relapses and those with any response on PET scan (CMR or PMR) have a lesser risk of future relapses. Larger studies are required to confirm this finding.

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