SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2008; 25; 143-150

^{18}F-FDG PET in sarcoidosis: an observational study in 12 patients treated with infliximab

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Abstract. *Background:* ^{18}F-FDG PET is a promising technique in sarcoidosis imaging, although it is not incorporated in routine activity assessment. The purpose of this study was to correlate ^{18}F-FDG PET with standard sarcoidosis activity parameters during infliximab treatment. *Methods:* Twelve patients with refractory sarcoidosis were treated with 6 cycles of infliximab. Pre- and post-therapy ^{18}F-FDG PET was visually evaluated and SUV_{max} was measured. In addition, the effect of infliximab was evaluated by changes in symptoms, angiotensin converting enzyme (ACE), soluble interleukin-2 receptor (sIL-2R), vital capacity (VC), diffusion capacity of the lung for carbon monoxide (DLCO) and chest radiography. SUV_{max} and conventional parameters were correlated. *Results:* Clinical improvement as judged by conventional parameters was seen in all patients, though with a minor response in one. Symptoms improved in 11/12 patients while chest radiographic stages did not change. The decrease in ACE was 39% and in sIL-2R 47% ($p<0.01$). Improvement of VC and DLCO was 5.4% and 3.3% ($p<0.05$), respectively. ^{18}F-FDG PET revealed either improvement or normalization in 11/12 (92%) clinically responding patients. The overall decrease in SUV_{max} was 55% ($p<0.01$); the patient with a limited response showed a 34% increase. A decrease in SUV_{max} of the lung parenchyma correlated with an improvement of VC ($r=-0.75$, $p<0.01$). No significant correlation between SUV_{max} and other parameters was found. *Conclusion:* Changes imaged by ^{18}F-FDG PET during infliximab treatment in sarcoidosis patients correlate with signs of clinical improvement to a considerate extent, which supports the hypothesis that ^{18}F-FDG uptake represents disease activity. *(Sarcoidosis Vasc Diffuse Lung Dis 2008; 25: 143-150)*

Key words: ^{18}F-FDG PET, sarcoidosis, infliximab, pulmonary function tests, biological markers

Introduction

Sarcoidosis is a multi organ disease, characterized by the presence of epitheloid cell granulomas. The formation of these granulomas is, among others, regulated by tumor necrosis factor (TNF)-α (1). Anti-TNF-α has already shown to be an effective therapy in other TNF-α mediated conditions e.g., rheumatoid arthritis, inflammatory bowel disease and ankylosing spondylitis (2-4). Several studies indicate that TNF-α therapy might also be useful in the treatment of severe pulmonary and extra pulmonary sarcoidosis (5-7).

To determine the effect of anti-TNF-α in sarcoidosis, several parameters can be used such as the evaluation of symptoms, serum concentrations of angiotensin-converting enzyme (ACE), soluble interleukin-2 receptor (sIL-2R), pulmonary function tests (PFT) and chest radiography. However, each activity parameter has its limitation. Symptoms might be difficult to interpret; especially fatigue is a very common

Received: 29 September 2008
Accepted after Revision: 26 November 2008
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and persisting symptom in sarcoidosis patients (8). ACE is an unattractive tool due to its moderate sensitivity (9) and cannot be used as a reliable follow-up tool (10). sIL-2R appears somewhat more reliable but is not widely available (11, 12). An improvement of PFT is likely to reflect a positive therapeutic effect. However, persistent abnormal PFT might represent an ineffective drug, an inadequate dosage or even irreversible fibrotic changes. Despite these shortcomings, decisions regarding treatment and treatment monitoring are currently based on a combination of the aforementioned parameters.

Fluor-18 deoxyglucose (^{18}F-FDG) PET is thought to represent the active granuloma in sarcoidosis and it has already shown to be a sensitive tool in the assessment of this disease (13-15). The use of ^{18}F-FDG PET as an imaging tool to evaluate infliximab treatment has not been described previously. The aim of this study is to correlate changes in ^{18}F-FDG PET with conventional activity parameters in sarcoidosis patients during anti-TNF-α therapy in order to illustrate that ^{18}F-FDG uptake indeed represents active disease and might be used to monitor therapeutic effects.

Materials and Methods

Patients

Nineteen biopsy proven sarcoidosis patients who had received infliximab in the St Antonius Hospital Nieuwegein were evaluated. Three patients had a Gallium-67 scan prior to therapy, one patient had a common variable immunodeficiency and one patient received only 3 cycles of infliximab due to psychiatric problems. One patient had cardiac sarcoidosis and one patient neurosarcoidosis, both without other signs of sarcoidosis based on ^{18}F-FDG PET. Since the brain and heart show a high physiologic uptake of ^{18}F-FDG and the role of ^{18}F-FDG PET in neuro- and cardiac sarcoidosis has not been elucidated yet, these patients were not included.

In total, 12 sarcoidosis patients treated with infliximab between March 2005 and September 2007 were included in this retrospective study. All patients had therapy resistant sarcoidosis or did not tolerate conventional therapy. Active or latent tuberculosis was excluded in all patients. Infliximab was administered in a dose of 5 mg/kg bodyweight in week 0, 2, 6, 12, 18 and 24 (5). During infliximab treatment, no additional therapy was started and dosages of currently used drugs were maintained at the same level.

This study was approved by the local medical ethical committee.

Evaluation of the infliximab effect by conventional parameters

At the time of inclusion, all symptoms were described in the patients medical record as well as their smoking status and prior use of immunosuppressive drugs. Serum ACE and sIL-2R were simultaneously obtained, vital capacity (VC) and diffusion capacity of the lung for carbon monoxide (DLCO) were performed and chest radiography was made. Symptoms were evaluated at the time of the last infliximab treatment and all previously mentioned parameters of disease activity were repeated.

ACE was corrected for genotype (16). ACE was considered normal or increased in accordance with genotype corrected reference values. Reference value for I/I was 9-43 U/l, for I/D 14-62 U/l and for D/D 24-82 U/l. Serum sIL-2R above 700 U/ml was considered increased. PFT was defined as the percentage predicted and the absolute change in percentage predicted VC and DLCO was used to evaluate the effect.

The pulmonologist determined the effect of infliximab based on the changes of the above mentioned parameters.

^{18}F-FDG PET

The patient fasted for at least six hours and before the intravenous injection of ^{18}F-FDG, 5 milligram of diazepam was administered orally to reduce muscle activity and appearance of brown fat. In order to reduce radiation exposure and accelerate ^{18}F-FDG excretion by the kidneys, 20 milligrams of furosemide was injected intravenously. This was followed by 295-400 MBq ^{18}F-FDG (Covideon, Petten, the Netherlands). 295 MBq was given to patients with a body weight less than 80 kilograms. When the body weight exceeded 80 kilograms a calculated dose was used (body weight /10 * 37 MBq) with a maximum of 400 MBq. PET was performed using the Philips Allegro PET system with external Cesium-137 source for transmission scanning (Philips Medical

Systems, Eindhoven, the Netherlands). Sixty minutes after administration of ^{18}F-FDG, transmission scan was started followed by emission scans from the subinguinal region to the head. Acquisition time per bed position was three minutes.

Two independent nuclear medicine physicians, blinded for all clinical data, interpreted ^{18}F-FDG PET. In case of disagreement between the observers, a third nuclear medicine physician interpreted the images and final conclusion was based on majority of votes.

^{18}F-FDG PET was visually evaluated. Disease activity was assessed separately in the mediastinum, hila, lung parenchyma, extra pulmonary lymph nodes, liver, spleen, bone marrow, skeletal and muscles. These sites were scored either positive or negative (positive = increased ^{18}F-FDG uptake, negative = no increased ^{18}F-FDG uptake). In addition, quantitative assessment was performed, based on maximum standardized uptake value (SUV_{max}) corrected for body weight. To correlate ACE and sIL-2R with SUV_{max}, the maximum change of SUV_{max} in any of the affected organs was used because these serum parameters are thought to represent the total granuloma load (17). VC and DLCO were correlated with changes in SUV_{max} measured in the lung parenchyma.

Statistical analysis

Paired samples t-test was used to compare pre and post therapy values. A two-sided p-value < 0.05 was considered to be statistically significant. Correlations between ACE, sIL-2R, VC, DLCO and SUV_{max} were determined using Spearman's rank. Data are presented as mean values ± standard deviation. The statistical evaluation was performed using SPSS 15 (SPSS Inc, Chicago, IL, USA).

There has been no external funding source for this study.

Results

Patients

Patients' characteristics are summarized in table 1. Chest radiographic stage I disease was seen in 3 patients. Besides pulmonary involvement, these patients had severe extra pulmonary sarcoidosis for which infliximab was indicated. Two patients suffered from a visual loss due to uveitis and optic neuritis, respectively. The third patient had extensive muscle and skin involvement.

Table 1. Patient characteristics at baseline

	n = 12
Age (years)	43.6 (± 9.3)
Female/Male	6 / 6
Smoking	
Never	8
Ex-smoker	4
Disease duration (years)	3.9 (± 3.1)
Pulmonary function tests (% predicted)	
VC	85% (± 19)
DLCO	61% (± 18)
Chest radiographic stage	
I	3
II	6
III	2
IV	1
Prior therapy	
Prednisone	1
Methotrexate with prior use of prednisone	3
Prednisone and methotrexate	7
Prednisone and plaquenil	1

Evaluation of the infliximab effect by conventional parameters

Changes in symptoms, serum ACE and sIL-2R, VC and DLCO after completion of the final infliximab treatment are shown in table 2.

Although not validated by a standardized dyspnoea score or a 6-minute walk-distance test, 11 patients noticed an improvement of prior symptoms. One patient did not notice any improvement and PFT remained about the same level while the serological markers showed a dramatic decrease.

Prior to therapy, there were 6 patients with a normal ACE and only one patient with a normal sIL-2R. An average decrease of 40 U/l (± 43) was found for ACE (p < 0.01), representing a decrease of 39% (± 27). One patient showed an increase of ACE, however, still within the normal range. Eleven patients did show a decrease and 5 of these patients already had a normal ACE prior to infliximab treatment. Despite a decrease during treatment, 2 of the 11 patients still had an elevated ACE after the final infliximab treatment.

An average decrease of 902 U/ml (± 753) was found for sIL-2R (p < 0.01), representing a decrease

Table 2. Changes in chest radiography, serological markers, pulmonary function tests and symptoms during infliximab treatment

Patient	Symptoms prior to therapy	Chest radiographic stage	Chest radiographic changes during treatment	ACE	sIL-2R	VC	DLCO	Symptoms
Total				-39%*	-47%*	+5.4%*	+3.3%*	
1	Fatigue, coughing, weight loss	II	Improvement of interstitial abnormalities	-46% †	-73%	+6%	+12%	Improved
2	Dyspnea, coughing	IV	Decrease of lymphadenopathy	-47% †	-62%	-5%	+3%	No change
3	Fatigue, visual loss due to neuritis optica	I	No changes	-33% †	-69%	+7%	-3%	Improved
4	Dyspnea d'effort, thoracic pain	II	Decrease of lymphadenopathy and improvement of interstitial abnormalities	-47%	-72%	+11%	-3%	Improved
5	Fatigue, dyspnea d'effort	III	No changes	-12% †	-40%	+15%	+4%	Improved
6	Fatigue, dyspnea, muscle pain in arms and legs	I	Decrease of lymphadenopathy	-53% †	-52% ‡	+5%	-1%	Improved
7	Fatigue, dyspnea d'effort, thoracic pain	II	No changes	-49%	-11% ‡	+4%	+3%	Improved
8	Fatigue, visual loss due to uveitis	I	Decrease of lymphadenopathy	-57%	-80%	-5%	+3%	Improved
9	Dyspea d'effort, stridor, coughing	II	No changes	+18% †	+34% †	+10%	+4%	Improved
10	Fatigue, dyspnea, coughing, skin lesions	III	No changes	-72% ‡	-76%	+5%	+11%	Improved
11	Fatigue, dyspnea, arthralgia	II	No changes	-66%	-72% ‡	+7%	+8%	Improved
12	Fatigue, coughing, night sweating, abdominal pain, arthralgia	II	Improvement of interstitial abnormalities	-3% ‡	+6% ‡	+5%	-2%	Less fatigue, other symptoms did not improve

ACE = angiotensin-converting enzyme, sIL-2R = soluble interleukin-2 receptor, VC = vital capacity, DLCO = diffusion capacity of the lung for carbon monoxide
* = statistically significant, † = normal pre infliximab level, ‡ = abnormal post infliximab level

of 47% (± 37). Two patients showed an increase of sIL-2R; one within the normal range. Ten patients showed a decrease of sIL-2R, all with an elevated sIL-2R level prior to therapy. Three of these 10 patients still had an abnormal sIL-2R after the final infliximab treatment.

Overall, an increase in VC of 5.4% (± 5.8) was found ($p < 0.01$). DLCO showed an improvement of 3.3% (± 5.1), which was also statistically significant ($p < 0.05$). Ten patients showed an increase of VC with an average increase of 7.5% in this subgroup (range 4%-15%). Two patients showed a decrease of VC of 5.0%. Eight patients showed an improvement of DLCO with an average increase of 6.0%. Four patients showed a decrease of DLCO ranging between 1%-3%.

Chest radiographic stages did not change during infliximab treatment. However, 6 patients did show an improvement; in 3 patients there was a decrease of lymphadenopathy, in 2 there was an improvement of interstitial abnormalities and one patient showed both signs of improvement.

Based on the above mentioned conventional activity parameters, 11 patients were considered to benefit from the infliximab treatment. In one patient (patient 12), infliximab appeared to have a minor clinical effect.

^{18}F-FDG PET

Pre and post infliximab ^{18}F-FDG PET results are illustrated in table 3. Pre infliximab ^{18}F-FDG PET was abnormal in all patients. Involvement of the pulmonary tract was seen in all 12 patients, while 8 patients showed extra pulmonary involvement.

The average interval between ^{18}F-FDG PET and the final infliximab treatment was 2.8 weeks

Table 3. Pre and post therapy localizations of increased ^{18}F-FDG uptake and change in SUV_{max}

Patient	Pre therapy ^{18}F-FDG PET	Post therapy ^{18}F-FDG PET	Maximum change in SUV_{max}
1	med-hila-par-bone marrow*	normalized	-83%
2	med-hila-par	normalized	-12%
3	med-hila-lnn	normalized	-83%
4	med-hila-par	normalized	-82%
5	med-hila-par	par	-78%
6	med-hila-par-muscles*	med-hila	-47%
7	med-hila-par-lnn	med-hila-par-lnn	-45%
8	med-hila-par-lnn-parotids	med-hila-par-parotids	-61%
9	med-hila-par	med-hila	-82%
10	med-hila-par-lnn-spleen-parotids	hila-par-spleen-parotids	-55%
11	med-hila-par-lnn	med-par	-66%
12	med-hila-lnn-liver*-muscles-aortic wall	med-hila-lnn-liver-muscles-aortic wall	+34%

med = mediastinum, par = lung parenchyma, lnn = lymph nodes, SUV_{max} = maximum standardized uptake value
* = histologically proven

(± 2.2). Four patients showed a normalized post infliximab ^{18}F-FDG PET (Fig. 1). Seven patients showed an improvement, while one patient did not show any change.

The overall decrease in SUV_{max} was 5.4 (± 5.0) corresponding with an average decrease of 55% (± 35) ($p < 0.01$). In all patients with a normalization or improvement, the average decrease in SUV_{max} was 63% (± 22). The one patient without any visual change on ^{18}F-FDG PET showed an increase in SUV_{max} of 34% (Fig. 2).

The average decrease in SUV_{max} of the lung parenchyma was 2.5 (± 3.7) which correlated with an improvement of VC ($r = -0.75$, $p < 0.01$) (Fig. 3). There was no significant correlation between SUV_{max} and DLCO, ACE or sIL-2R.

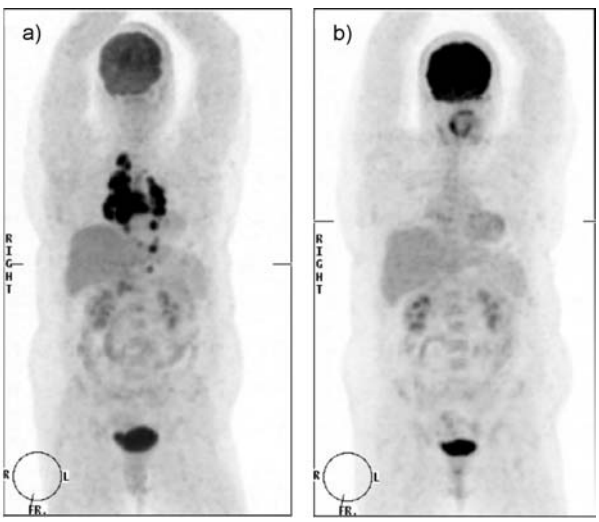

Fig. 1. Baseline 18F-FDG PET (a) of patient number 3 shows increased metabolic activity in the mediastinum, hila and para-aortic lymph nodes. Post infliximab 18F-FDG PET (b) shows a normalization together with a decrease of serum ACE and sIL-2R, improvement of symptoms and VC

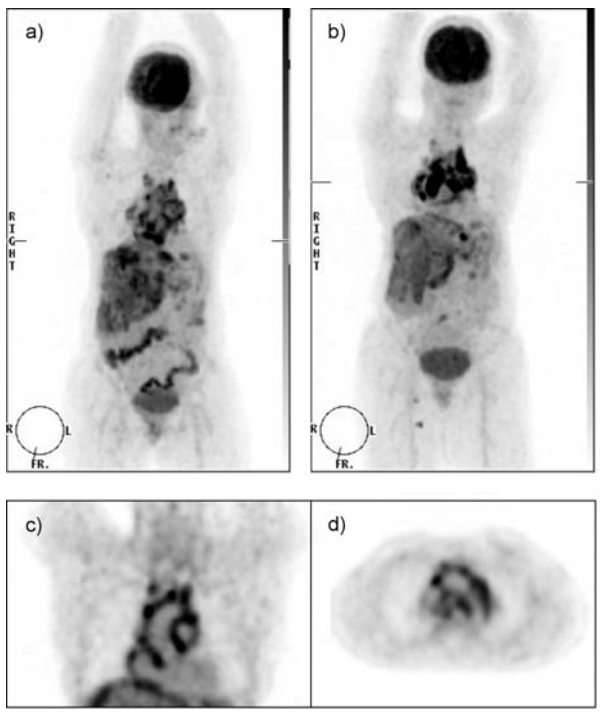

Fig. 2. 18F-FDG PET of patient number 12 before (a) and after (b) infliximab treatment. There is increased metabolic activity in the mediastinum, hila, lymph nodes, liver, ascending aorta (c) and arcus aortae (d). The increased uptake in the aorta might indicate an aortitis. SUVmax of the thoracic abnormalities showed an increase of 34% after infliximab treatment. Clinically, this patient showed a minor, pulmonary improvement.

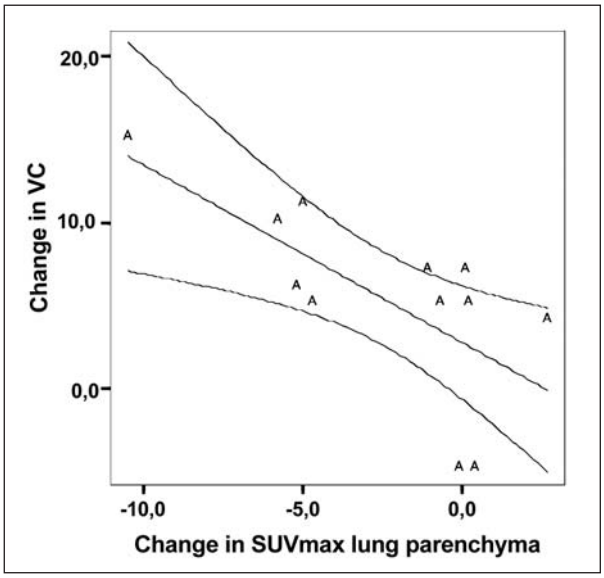

Fig. 3. Correlation between change in SUV_{max} in the lung parenchyma and VC. Spearman's rho was -0.75 ($p < 0.01$). The lines represent the mean with 95% confidence interval.

Discussion

In this case series of sarcoidosis patients treated with infliximab, visually evaluated ^{18}F-FDG PET activity correlated with signs of clinical improvement in 11/12 patients. All patients with a clear clinical improvement based on a combination of conventional activity parameters demonstrated an improvement or even normalization of ^{18}F-FDG PET. The patient with a minor clinical response showed no visual change on ^{18}F-FDG PET, while SUV_{max} showed an increase. The current study shows an overall decrease in SUV_{max} of 55% with a significant correlation between the decrease in SUV_{max} measured in the lung parenchyma and an improvement of VC.

The use of corticosteroids and its effect imaged by ^{18}F-FDG PET were previously described in a small patient population (15). To our knowledge, this is the first observational study that illustrates a simultaneous decrease in metabolic activity and an improvement of clinical signs during the use of anti-TNF-α therapy. Although this is a retrospective analysis in a selected patient population, these results seem to confirm our hypothesis that ^{18}F-FDG uptake in sarcoidosis represents active disease. At the same time, this study might suggest the use of ^{18}F-FDG PET as a management tool during therapy although additional research is necessary to validate this hypothesis.

In one patient, a pulmonary improvement was exhibited though ^{18}F-FDG PET did not adequately reflect this effect (Fig. 2). However, the initial effect of infliximab achieved in this patient was considered to be limited. Previously increased ACE, sIL-2R, serum aminotransferase and bilirubin remained unchanged and despite less fatigue there was no improvement of the other symptoms. The lack of clinical response was considered to justify a higher dosage of infliximab (7.5 mg/kg bodyweight per 4 weeks) which resulted in an improvement of all symptoms, a significant decrease or normalisation of ACE, sIL-2R, serum aminotransferase and bilirubin, and an increase in VC of 13% and DLCO of 6%. Although the initial minor pulmonary improvement was not properly reflected by ^{18}F-FDG PET, ^{18}F-FDG PET performed after the second series of infliximab, demonstrated an improvement at all sites with previously increased metabolic activity. Because of the abovementioned course of the disease, we believe that this imaging technique, even in this specific patient, adequately reflects the actual activity state.

Because the results of ^{18}F-FDG PET in these 12 patients correlate with the analysis of conventional activity markers in a considerate extent, the additional role of this imaging technique appears to be limited. However, the difficulty of sarcoidosis activity assessment is illustrated when the effect of infliximab is evaluated in the individual patient.

ACE showed an average decrease of 39%, although 6 patients (50%) already showed a normal ACE level prior to infliximab therapy. sIL-2R showed an average decrease of 47% and seemed somewhat more compatible with the patients sarcoidosis activity state. Overall, pulmonary function tests showed a significant improvement of 5.4% for VC and 3.3% for DLCO. However, in 6 patients the positive change in VC was accompanied by a negative change in DLCO or vice versa. In addition, this study illustrates the limitations of chest radiography as 6 patients showed an improvement of symptoms and pulmonary function tests without any change in chest radiography. Chest radiographic stages did not change in any of the 11 clinically responding patients.

Even though infliximab therapy resulted in an overall decrease in biological markers and improve-

ment of symptoms and pulmonary function tests, the individual results can be misleading as illustrated in our patient population. This dictates cautiousness in interpreting the effect of infliximab based on conventional parameters because this might lead to the underestimation of a potentially useful treatment in a sometimes devitalizing disease.

Baughman et. al. performed a randomized, double blind, placebo controlled study to evaluate infliximab therapy in sarcoidosis patients (5). An increase in FVC of 2.5% was found as well as a decrease in reticulonodular opacities on chest radiography. Subgroup analysis showed a larger improvement in patients with longer disease duration, lower FVC or more symptoms. In addition, infliximab was more effective in patients receiving immunosuppressive drugs, higher doses of corticosteroids or in patients with multiple extra pulmonary lesions.

Differences in response to infliximab were also observed in patients with ankylosing spondylitis. In this patient population, three types of responders were observed during treatment: early clinical remission, persistent low disease activity and limited improvements (4).

In order to evaluate the effect of infliximab in sarcoidosis patients and perhaps customise treatment, a tool to monitor the effect of this expensive therapy might be desirable. In non-Hodgkin's lymphoma patients, ^{18}F-FDG PET has already proven to be a guide in therapy management by evaluating the chemotherapy effect after 1 or 2 cycles (18, 19). The metabolic response in non-Hodgkin's lymphoma patients is correlated with treatment failure and disease free survival (19). To assess the potential guiding role of ^{18}F-FDG PET during infliximab treatment in sarcoidosis, a prospective and blinded study with a larger patient population is needed.

In conclusion, changes in ^{18}F-FDG PET correlate with signs of clinical improvement in sarcoidosis patients during infliximab treatment to a great extent. There is even a significant correlation between the decrease in SUV_{max} of the lung parenchyma and improvement of VC. The current study seems to confirm that ^{18}F-FDG uptake in sarcoidosis represents active disease and might warrant additional research to evaluate the potential role of ^{18}F-FDG PET in sarcoidosis management.

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