Comparison of 18F-FDG PET/CT findings with current clinical disease status in patients with Takayasu’s arteritis

I. Karapolat¹, M. Kalfa², G. Keser², M. Yalçin¹, V. Inal², K. Kumanlioğlu³, T. Pirildar⁴, K. Aksu⁴

ABSTRACT

Objective. 18F-fluorodeoxyglucose-positron emission tomography/computed tomography (18F-FDG PET/CT) scanning has been proposed as a new tool to assess disease activity in Takayasu arteritis (TA). We investigated whether 18F-FDG PET/CT findings were consistent with current clinical disease status in patients with TA.

Methods. In this cross sectional study, 22 patients with TA were enrolled. Clinical disease activity was assessed by the combination of National Institutes of Health (NIH) criteria, Disease Extent Index-Takayasu (DEI-Tak) score, physician global assessment and 18F-FDG PET/CT scans.

Results. At the time 18F-FDG PET/CT scans were taken, the majority of the patients (17/22) were using immunosuppressive (IS) drugs, and only four patients had clinically active disease. 18F-FDG PET/CT scans confirmed the presence of active vasculitic lesions in those four patients. In 16 out of 18 patients who were accepted to be in clinical remission, 18F-FDG PET/CT scans were also normal. There were only two patients with discordant results, i.e. active 18F-FDG PET/CT findings despite the lack of clinical activity. Interestingly, clinical exacerbation occurred four weeks later in one of them. Overall sensitivity and specificity of 18F-FDG PET/CT findings for clinical activity were 100% and 88.9%, respectively.

Conclusion. We found that 18F-FDG PET/CT findings were generally consistent with clinical disease status in TA. Although use of IS drugs certainly impairs diagnostic accuracy of 18F-FDG PET/CT in TA, this imaging method may still have a potential for confirming remission or detecting disease activity in patients with TA receiving treatment.

Introduction

Takayasu arteritis (TA) is a rare, systemic vasculitis of unknown etiology, affecting mostly young females, having a chronic disease course and commonly involving large vessels such as the aorta and the branches of the aortic arch (1, 2). Although conventional angiography has been the gold standard for the diagnosis of TA, assessment of disease activity remains a challenge (1-4). Since TA is a chronic autoimmune disease requiring long-term use of corticosteroids and immunosuppressive (IS) drugs, assessment of disease activity is very important to tailor the dose of treatment (4). Although constitutional symptoms, clinical findings and some laboratory parameters including acute-phase reactants and haemoglobin levels may be helpful in some cases, these parameters may be misleading in other patients (1, 3). In other words, assessment of disease activity is not straightforward, and 45–50% of the patients considered to be in clinical remission, may be histologically active (1, 3-5).

Traditionally, National Institutes of Health (NIH) criteria, also known as Kerr’s criteria, defined in 1994 have been used to assess disease activity in TA (1). On the other hand, Disease Extent Index-Takayasu (DEI-Tak) has recently been defined for the follow-up of TA, assessing only clinical findings without the requirement for imaging techniques (6). Recently, DEI-Tak was also shown to be a practical, valuable tool to assess disease activity and progression in a Turkish TA series (7).

Imaging methods may also be useful to detect disease activity (8). Since conventional angiography is an invasive method, it cannot be used for serial follow-up. Besides, this method can only show new radiological lesions affecting the vessel lumen, but not current disease activity (1, 8). Other imaging

Competing interests: none declared.
modalities such as magnetic resonance angiography (9), computed tomography (CT) (10), ultrasonography (11) and 18F-Fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) (12-14) seem to be promising in this aspect. Among these, 18F-FDG PET/CT is a non-invasive, metabolic imaging method that measures 18F-FDG, which accumulates in hypermetabolic cells (15). Since large-vessel inflammation is the hallmark of TA, 18F-FDG is expected to accumulate in inflamed vessels based upon the increased glucose transport and glycolysis of activated inflammatory cells infiltrating these vessels (16-18). Therefore, 18F-FDG PET/CT has the potential to reflect active vascular inflammation, and in literature there are studies investigating the role of 18F-FDG PET or PET/CT in the diagnosis or in the assessment of disease activity of large-vessel vasculitides, including TA (14, 19-25). In a recent review covering new developments in systemic vasculitis, 18F-FDG PET and PET/CT were discussed among promising noninvasive imaging modalities which may be used for the diagnosis of large-vessel vasculitides (24). Similarly, the role of 18F-FDG PET or PET/CT in the assessment of disease activity and progression of TA was elegantly reviewed by Direskeneli et al. (25).

Some TA patients receiving IS drugs may still have active vascular lesions despite apparent clinical remission (4, 5). In this aspect, 18F-FDG-PET/CT scans may confirm clinical remission or may show active vascular disease, thereby allowing more accurate adjustment of IS drug doses. Therefore, the aim of the present study was to find out whether 18F-FDG-PET/CT findings in patients with TA were consistent with current clinical disease activity. While in previous studies clinical disease activity was mostly assessed using NIH (Kerr’s) criteria (1) and acute phase responses, in the present study DEI-Tak scores (6) were additionally used. In other words, 18F-FDG-PET/CT findings in TA were compared with clinical disease activity evaluated using a combination of NIH criteria, DEI-Tak scores, acute phase responses and physician global assessment (PGA).

### Materials and methods

#### Patients

In this cross sectional study, 22 patients (F/M 20/2, mean age 40.5 (range 18-56) years, mean disease duration 6.0 (range 1-28) years), fulfilling the 1990 American College of Rheumatology (ACR) criteria for TA (26) and being followed up at Ege University Rheumatology Outpatient Department were enrolled. Patients with abnormal liver function tests or concomitant diabetes mellitus were excluded. In other words, fasting serum glucose, aspartate aminotransferase and alanine aminotransferase levels were normal. Patients with other large-vessel vasculitides were not included in this study. The present study was carried out between January 2011 and February 2012, and was approved by the local ethics committee (CBU/application no. 269). Informed consent was obtained from all patients who participated in this study.

The past medical records were available for all of the patients. The diagnosis of TA was confirmed by conventional angiography in all patients. The angiographic findings were grouped according to the angiographic classification for TA, defined at the International Conference on TA in Tokyo in 1994 (27). The arteriographic classification was as follows: Type I involved branches of aortic arch, Type IIa involved ascending aorta, aortic arch and its branches, Type IIb a combination of Type IIa and the involvement of thoracic descending aorta, Type III involved the thoracic descending aorta, the abdominal aorta and/or renal arteries, Type IV involved only the abdominal aorta and/or renal arteries, Type Va was combination of Type IIa and Type IV (27).

#### Clinical assessment of disease activity

Current clinical disease activity was assessed using both NIH (Kerr’s) criteria and DEI-Tak. Current acute phase responses including erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) levels and PGA were also noted. Then all the patients were referred to the Nuclear Medicine Department of Sifa University for 18F-FDG PET/CT imaging.

### 18F-FDG PET/CT

#### Acquisition of image

Whole-body 18F-FDG PET/CT was performed using a PET/CT scanner (HI-REZ Biograph 6, SIEMENS) an hour after intravenous injection of approximately 13 mCi of F-18 labelled fluorodeoxyglucose (18F-FDG). A CT scan without contrast agent was performed, covering the area from the vertex to the proximal thigh, and the images were used for attenuation correction and image fusion. This was followed by whole-body 3D PET acquisi-
**Table I.** Comparison of 18F-FDG PET/CT positive and negative groups with regard to demographic, clinical, and laboratory data.

<table>
<thead>
<tr>
<th>Demographic and clinical features</th>
<th>18F-FDG PET/CT positive n:6</th>
<th>18F-FDG PET/CT negative n:16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (median (min-max))</td>
<td>46 (18-56)</td>
<td>39.50 (21-54)</td>
</tr>
<tr>
<td>Sex (F)</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Smoking (positive) (n, %)</td>
<td>2 (33.3)</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td>Duration of disease (years) (median (min-max))</td>
<td>2 (1-4.5)</td>
<td>6 (1-28)</td>
</tr>
<tr>
<td>Angiographic classification (n, %)</td>
<td>Type 1: 1 (16.7)</td>
<td>7 (43.8)</td>
</tr>
<tr>
<td></td>
<td>Type 2a: 1 (16.7)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Type 5: 0</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td></td>
<td>Type 6: 4 (66.7)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>Constitutional symptoms (n, %)*</td>
<td>4 (66.7)</td>
<td>2 (14.5)</td>
</tr>
<tr>
<td>NIH (Kerr’s) Criteria (active disease based upon presence of at least two criteria)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>DEI-Tak score (mean±SD)</td>
<td>5 ± 2.45</td>
<td>0</td>
</tr>
<tr>
<td>Physician Global Assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>4 (66.7)</td>
<td>0</td>
</tr>
<tr>
<td>Grumbling or persistent disease</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inactive</td>
<td>2 (33.3)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Laboratory findings (median (min-max))</td>
<td>20.50 (8-140)</td>
<td>13.50 (3-25)</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>2.31 (0-3)</td>
<td>1.52 (1-1.9)</td>
</tr>
<tr>
<td>Patients receiving IS drugs(n, %)</td>
<td>3 (50)</td>
<td>14 (87.5)</td>
</tr>
</tbody>
</table>

*ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; IS: Immunosuppressive. NIH: National Institute of Health; DEI-Tak: Disease Extent Index-Takayasu.

**Table II.** Results of 18F-FDG PET/CT and overall clinical disease activity as assessed by the combination of NIH criteria, DEI-Tak scores, physician global assessment and acute phase responses.

<table>
<thead>
<tr>
<th></th>
<th>Clinically Active</th>
<th>Clinically Inactive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>18F-FDG PET/CT-positive</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>18F-FDG PET/CT-negative</td>
<td>0</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>18</td>
<td>22</td>
</tr>
</tbody>
</table>

**Interpretation of data**

18F-FDG PET/CT scans were evaluated by a single nuclear medicine physician having European Board of Nuclear Medicine certificate and who was blinded to clinical data (I.K.). Since there are many factors which might influence the quantitative SUV, including body habitus, serum glucose level, uptake time, partial volume effect, imaging system parameters, reconstruction parameters, radiopharmaceutical distribution geometry and region-of-interest geometry (28), in the present study we used the semi-quantitative visual assessment of 18F-FDG uptake in the vascular wall using liver uptake as an internal reference of uptake in cases without liver disease. The intensity of the 18F-FDG uptake on the walls of aorta and its main branches (ascending aorta, aortic arch, descending thoracic aorta, abdominal aorta, subclavian artery, brachiocephalic artery and common carotid artery) and the pulmonary arteries were visually assessed. As in the previous studies, a semi-quantitative visual grading system was used (22). Briefly, uptakes were graded using a 4-point scale: 0=uptake equal to mediastinal blood pool activity; 1=low-grade uptake, lower than liver; 2=intermediate-grade uptake equal to the liver; and 3=high-grade uptake higher than the liver. Uptakes higher than grade 1 in the thoracic aorta and higher than grade 0 in any other vessel were considered active vasculitis. Besides, quantitative analysis using the maximum standardised uptake value (SUVmax), defined as the ratio of 18F-FDG activity to injected activity normalised to body mass was also performed. SUV was reported to have limitations for comparing disease activity between individual patients although it might be valuable in follow-up of disease activity in the same patient (22, 28). To minimise the effects of time from injection to acquisition and blood glucose level, mean liver SUV and maximum vascular uptake were determined from a liver region of interest (ROI) and a vascular ROI, respectively. Then, quantitative index (uptake intensity), which is defined as the ratio of vascular SUVmax to liver SUVmean was calculated.

**Statistical analyses**

The results were analysed using the Statistical Package for Social Sciences (SPSS), version 19.0 for Windows. Continuous variables were compared between groups (group 1: 18F-FDG PET/CT positive; group 2: 18F-FDG PET/CT negative) using the Mann-Whitney U-test. Categorical variables were compared using the Chi-square test. The Spearman test was used in the correlation analysis. A p-value below 0.05 was considered statistically significant.

**Results**

Demographic, clinical and laboratory data of TA patients with and without active 18F-FDG PET/CT findings were presented in Table I. Among 22 TA patients included in this cross-sectional study (F/M 20/2, mean age 40.5 years, mean disease duration 6.0 years), the majority of the patients (17/22) were using IS drugs at the time 18F-FDG PET/CT scans were taken. Only 4 patients had active disease (Table II). There was no doubt about clinical activity in those 4 patients, because both NIH (Kerr’s) criteria and DEI-Tak scores (mean±SD: 5±2.45), as well as PGA were concordant with respect to clinical disease activity. Among those 4 patients, 3 were
newly-diagnosed patients receiving no IS treatment, while the fourth one had already been under IS treatment. 18F-FDG-PET/CT scans showed active vascular lesions in all of these 4 patients (Fig. 1-2). The involved arteries, FDG-PET vascular visual scores, FDG-PET Vascular SUVmax and other technical details were given in Table III.

On the other hand, the remaining 18 patients were accepted to have no clinical disease activity, based upon the combination of NIH criteria, DEI-Tak scores, PGA, ESR and serum CRP levels. In 16 out of 18 patients, 18F-FDG PET/CT scans were also normal. However, there were 2 patients with discordant results. In other words, active 18F-FDG PET/CT findings were detected in 2 patients despite the lack of clinical activity. Interestingly, one

Fig. 1. Shows PET/CT fusion and CT images of a 57 year old female patient with increased 18F-FDG uptake in the left main carotid artery, brachiocephalic artery and aortic arch consisted with active vasculitis.

Fig. 2. Shows PET/CT fusion and CT images of a 52 year old female patient with increased 18F-FDG uptake in the aortic arch and descending thoracic aorta consisted with active vasculitis.
of these patients experienced exacerbation of clinical activity 4 weeks after the 18F-FDG PET/CT scan was performed. However the last patient remained inactive, despite active 18F-FDG PET/CT findings. Overall, regardless of clinical disease activity, there were 6 patients with positive 18F-FDG PET/CT findings (Table II). Statistical analysis showed that 18F-FDG PET/CT had a sensitivity of 100% specificity of 88.9%, a positive predictive value of 66.7% and a negative predictive value of 100%.

DEI-Tak scores, frequency of constitutional symptoms, ESR and serum CRP levels were significantly higher in TA patients with positive 18F-FDG PET/CT findings compared to those with negative findings (p<0.05). We also found that the duration of the disease was shorter in 18F-FDG PET/CT positive patients.

Mean 18F-FDG PET values were found to be significantly correlated with disease activity according to NIH criteria, DEI-Tak scores and active disease based upon PGA (p<0.05). However, ESR and CRP levels were not correlated with mean 18F-FDG PET values (p>0.05).

**Discussion**

Given that radiological and clinical data do not always correlate in TA (1, 4, 5), in the present cross-sectional study, F-18 FDG PET/CT scan findings in TA were compared with clinical disease activity assessed using the combination of NIH Criteria, DEI-Tak score, acute-phase reactants and PGA. We found out that 18F-FDG PET/CT findings were mostly consistent with clinical disease activity, having sensitivity and specificity values of 100% and 88.9%, respectively. Most of the TA patients included in this study were under IS treatment. Only four patients were clinically active and 18F-FDG PET/CT scans showed active vascular lesions in all of these patients, further confirming clinical activity. The remaining 18 TA patients were clinically inactive. Among these patients, active 18F-FDG PET/CT findings suggesting ongoing large-vessel inflammation were detected only in two patients. Interestingly, disease activity exacerbated in one of these patients nearly four weeks after the 18F-FDG PET/CT scan was performed. In other words, 18F-FDG PET/CT scan findings seemed to predict disease exacerbation in this patient. However the other patient remained inactive, despite active 18F-FDG PET/CT findings.

In the present study, we found that mean 18F-FDG PET values were not correlated with ESR and CRP. Indeed, this finding may be related with the classical notion that ESR and CRP alone are not reliable parameters to reflect disease activity in TA (3). Therefore, in selective cases 18F-FDG PET/CT may be performed in order to confirm disease activity or remission in TA. We also found that the duration of the disease was shorter in 18F-FDG PET/CT positive patients. This may be due to suppression of vascular inflammation in the long term, as the result of cumulative IS treatment. In five out of six patients with active 18F-FDG PET/CT findings, there was increased uptake in the aortic arch. Since aortic arch and thoracic aorta show less age-related abnormal vascular uptake, positive findings in those regions are more sensitive for TA compared to other vessels (14). In the present study, we carried out both visual assessment using a four-point scale and quantitative measurement using maximum SUV for the interpretation and grading of 18F-FDG PET/CT images. The results were similar. Since,
semi-quantitative grading is easier and less time consuming, it is more convenient and practical to use this method. However, quantitative measurement using maximum SUV might have an added value in follow-up of disease activity in the same patient.

In the literature there are clinical studies investigating the role of 18F-FDG PET or PET/CT findings in the diagnosis, and/or in the assessment of disease activity and extent of disease in TA (14, 19-23). Most of these studies are retrospective, and some of them focused on patients with large-vessel vasculitis as a whole group including TA. In all of the previous studies, which we will briefly review in the following paragraphs, clinical disease activity in TA was defined using the NIH criteria. The main difference between DEI-Tak and NIH criteria is the lack of imaging data in DEI-Tak (6). NIH criteria have a low sensitivity for detecting active disease. Unfortunately DEI-Tak also has a low sensitivity in evaluating activity of large-vessel vasculitis, with false-negative results being reported in up to one-third of patients assessed against the comparator of physician’s assessment (7). In the present study, we used both NIH criteria and DEI-Tak scores and we believe that combination of NIH criteria with DEI-Tak may lead to a better estimation of disease activity in TA. However, International Consensus Conference on Outcome Measures in Rheumatology (OMERACT 2011) aired their views that the gold standard of assessment of large-vessel vasculitis should be new vessel involvement, and Grayson et al. reported that imaging methods were more sensitive and accurate than clinical assessment in defining new vessel involvement (29). Taken together, these findings may imply that imaging may have an edge over clinical assessment by questionnaires in determining disease activity of large-vessel vasculitis.

Andrews et al. reported that 18F-FDG PET/CT detected active vascular lesions in 5 of 6 patients with active TA defined by the NIH criteria (19). In another study, Webb et al. retrospectively evaluated 28 18F-FDG PET scans performed on 18 patients suspected of having TA (14). They reported that 18F-FDG PET achieved a sensitivity of 92%, a specificity of 100%, and negative and positive predictive values of 85% and 100%, respectively in the initial assessment of active vasculitis in TA. They concluded that 18F-FDG PET could be used to diagnose early disease, to detect active disease and to monitor the effectiveness of treatment (14). Similarly, Walter et al. investigated the role of 18F-FDG PET/CT in the diagnosis and for the assessment of disease activity and extent in 26 patients with large-vessel vasculitis (20). However, most of the patients included in his study had giant cell arteritis, while only 6 patients had TA. They also included an age and gender-matched reference group from the patients undergoing 18F-FDG PET/CT for malignancy. In this study, large-vessel 18F-FDG uptake was positively correlated with the level of acute phase reactants in patients with large-vessel vasculitis (20).

Arnaud et al. retrospectively reviewed 40 consecutive 18F-FDG-PET scans obtained from 28 patients with TA (21). For assessing clinical activity, they used NIH criteria, serum CRP and ESR levels. MRI was also used for radiologic evaluation of disease activity. However, they found no association between 18F-FDG vascular uptake intensity and clinical, biologic, or MRI assessment of disease activity. They found no statistical association between levels of acute-phase reactants and intensity of vascular FDG uptake. There was also no significant association between the semi-quantitative assessment of 18F-FDG uptake and the presence of vascular wall thickening, gadolinium uptake, or the presence of vascular wall oedema (21). In a recent study from Korea, performed by Lee et al., usefulness of 18F-FDG PET/CT in the assessment of disease activity was retrospectively investigated in 32 patients with TA (22). Disease activity was assessed clinically by the NIH criteria. At the time 18F-FDG PET/CT scans were taken, 10 patients had been receiving IS treatment, and overall 23 patients were clinically inactive. 18F-FDG PET/CT was found to have a sensitivity of 78% and specificity of 87% for clinical activity. The ESR and CRP levels were significantly higher in 18F-FDG PET/CT-positive patients than in negative patients. Likewise, the sensitivity of 18F-FDG PET/CT for detecting active disease was higher in patients with higher ESR values.

More recently, Fuchs et al. reported that 18F-FDG PET was a sensitive and specific imaging tool for large-vessel vasculitis, especially when performed in patients not receiving IS drugs (23). They concluded that 18F-FDG PET increased the overall diagnostic accuracy and had an impact on the clinical management in a significant proportion of patients.

The advantage of 18F-FDG-PET/CT over other diagnostic methods is that it can be applied to both detect large-vessel vasculitis and monitor response to IS treatment. More importantly, the majority of the TA patients were on IS medications, including corticosteroids. Such treatments may obviously decrease 18F-FDG uptake (30). We believe that this is a more important problem, when 18F-FDG PET/CT scan is used for the diagnosis of TA. In the present study, we used 18F-FDG PET/CT to find out whether findings were consistent with clinical evaluation in patients with established diagnosis of TA. Such patients are generally under IS treatment and IS medication-induced decrease in 18F-FDG uptake might indeed reflect decreased or totally disappeared histological vasculitic activity.
in the large vessels. Nonetheless, there is another problem which IS medications may cause. Since semi-quantitative evaluation of 18F-FDG uptake of the vessels was based upon liver 18F-FDG uptake, any liver pathology may disturb the evaluation. Although liver function tests were normal in all the study participants, we cannot exclude the possibility of hepatic toxicity due to IS drugs, which may affect hepatic 18F-FDG uptake. Another limitation of the study was the possible hyperglycemic effect of the corticosteroids which may also affect hepatic 18F-FDG uptake (31-32). Although fasting blood glucose levels were normal and none of the patients had overt diabetes mellitus, we cannot exclude the possibility of latent diabetes in the study participants. Finally, for technical and financial reasons, we could not perform additional MRI angiography in our patients.

Another point to discuss in the interpretation of vascular lesions in using 18F-FDG PET/CT is differentiating active vasculitic lesions from atherosclerotic lesions. The pattern and the level of vascular 18F-FDG uptake are obviously important for accurate interpretation. Intense and concentric vascular uptakes involving the aortic arch, ascending aorta and large cervical arteries strongly suggests a vascular inflammatory disease, while moderate and patchy vascular uptakes affecting the extremities may be consistent with atherosclerotic lesions (15).

Conclusion
18F-FDG PET CT has potential for development as a valuable tool for assessing TA disease activity. In the present study, 18F-FDG PET/CT findings were generally found to be consistent with current clinical disease status in TA. Although use of IS drugs certainly impairs diagnostic accuracy of 18F-FDG PET/CT in TA, this imaging method may still have a potential for confirming remission or detecting disease activity in patients with established diagnosis of TA and receiving IS drugs. Larger and prospective studies, comparing 18F-FDG PET/CT findings before and after IS treatment in patients with established diagnosis of TA may be needed.

References