ARTHRITIS & RHEUMATISM
Vol. 64, No. 3, March 2012, pp 866–875
DOI 10.1002/art.33413

The Role of ^{18}F-Fluorodeoxyglucose–Positron Emission Tomography in the Assessment of Disease Activity in Patients With Takayasu Arteritis

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Objective. **The assessment of disease activity in Takayasu arteritis (TA) is difficult in clinical situations because clinical symptoms and laboratory parameters do not always reflect the actual inflammation of the arterial wall. We undertook this study to comprehensively investigate the role of ^{18}F-fluorodeoxyglucose–positron emission tomography (FDG-PET) in the assessment of disease activity in patients with TA.**

Methods. **We performed a retrospective chart review of 53 FDG-PET scans in 38 patients with TA. We measured ^{18}F-fluorodeoxyglucose (^{18}F-FDG) accumulation in the vascular wall of the large vessel using semiquantitative (visual grade) and quantitative (standard uptake value intensity) analyses. Clinical disease activity was evaluated based on the National Institutes of Health criteria for active TA, and erythrocyte sedimentation rates (ESRs) and C-reactive protein (CRP) levels were measured.**

Results. **At baseline, active vascular ^{18}F-FDG uptake (visual grade ≥2) was observed in 18 of 24 patients with active disease and in 5 of 14 patients with inactive disease. There was a significant association between clinical disease activity and disease activity judged by FDG-PET ($P = 0.008$). Visual grade, standard uptake value intensity, and the number of vascular lesions with active ^{18}F-FDG uptake were significantly higher in patients with active disease and correlated well with the ESR and CRP levels. In 15 followup FDG-PET scans, the changes in visual grade, areas of active vascular ^{18}F-FDG uptake, and standard uptake value intensity reflected changes in clinical disease activity.**

Conclusion. **^{18}F-FDG uptake was associated with clinical disease activity and markers of inflammation, and FDG-PET reflected changes in clinical disease activity in patients with TA. FDG-PET may be a useful tool for aiding in the assessment of disease activity in patients with TA.**

Takayasu arteritis (TA) is a chronic inflammatory disease of the large arteries, primarily affecting the aorta and its main branches. Diagnosis of TA usually relies on postinflammatory sequels, such as narrowing, stenosis, or aneurysm of large vessels. Therefore, it is difficult to treat the potentially reversible early inflammation of TA before vascular insufficiencies occur. It is important to detect inflammation in the arterial wall early in the disease course and to treat it before irreversible structural changes occur. A sensitive and useful method is necessary for the diagnosis of early inflammation and for following disease activity in TA. However, assessment of disease activity in TA is difficult in clinical situations because the clinical symptoms and laboratory parameters do not always adequately reflect the actual inflammation of the arterial wall (1,2), and, as of now, no adequate surrogate is available for assessing disease activity in TA. Imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) reveal anatomic inflammatory changes of the affected arterial wall and have been suggested for mon-

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Submitted for publication November 24, 2010; accepted in revised form October 6, 2011.

itoring disease activity of TA (3), but have not shown consistent correlation with disease activity (4–7).

^{18}F-fluorodeoxyglucose–positron emission tomography (FDG-PET) is an imaging modality that visualizes the metabolic status of the body. It detects pairs of gamma rays emitted by ^{18}F-fluorodeoxyglucose (^{18}F-FDG), a positron-emitting radionuclide, taken up by cells with active metabolism such as malignant or inflammatory cells. Studies have shown the role of FDG-PET in diagnosing and monitoring TA, but there is some controversy regarding its ability to assess disease activity (8–15). Several studies showed that FDG-PET correctly detected active inflammation in the arterial wall of patients with TA, and that ^{18}F-FDG uptake decreased as disease activity improved (9–14). However, a recent study showed a lack of correlation between ^{18}F-FDG uptake and both clinical disease activity and markers of inflammation (8). Previous studies of the utility of FDG-PET had relatively small numbers of FDG-PET scans, mainly due to the rarity of TA (9–14). In this study, we investigated the role of FDG-PET in the assessment of TA disease activity in a relatively large cohort of patients with TA.

PATIENTS AND METHODS

Between December 2002 and January 2010, 38 consecutive patients diagnosed as having TA agreed to undergo at least 1 FDG-PET scan at Severance Hospital in Seoul, South Korea. FDG-PET scans were performed to evaluate baseline disease activity and to evaluate patients in whom disease activity was uncertain based on clinical and laboratory findings. We analyzed a total of 53 FDG-PET scans performed on these patients from July 2003 to February 2010; the median time from diagnosis of TA to the FDG-PET scan was 11 months (range 1–348 months). All of the patients met the American College of Rheumatology 1990 classification criteria for TA (16). We permitted the substitution of conventional angiography with either CT angiography or MR angiography, based on literature reporting the accuracy of CT and MRI in the diagnosis of TA (17–19). Approval by our institutional review board was obtained, and the requirement for informed consent was waived as this study was considered a diagnostic procedure with benefits for the patients.

PET examination. FDG-PET images were acquired using a whole-body tomography scanner (Allegro; Philips). This scanner provided a 57.6-cm axial field of view and an 18.5-cm transaxial field of view, which produced 46 image planes spaced 4.02 mm apart. The transaxial spatial resolution was 4.2 mm full width at half maximum at the center of the field of view, and the axial resolution was 5.0 mm full width at half maximum. The patients fasted for at least 6 hours before intravenous injection of 370 MBq (10 mCi) ^{18}F-FDG, and the mean serum glucose level was 92.9 mg/dl (range 74–122) just before injection. A whole-body emission scan was obtained in all patients 40–60 minutes after injection using the multiple-bed position technique. Seven to 8 bed positions from the external acoustic meatus to the thigh were imaged for 4 minutes per bed position. All patients were studied in the supine position with their arms alongside their bodies. Attenuation-corrected transaxial images were reconstructed with an iterative transmission algorithm called Row-Action Maximum-Likelihood 3D protocol using a 3-dimensional (3-D) image filter into a 128 $\times$ 128 matrix.

Analysis of FDG-PET images. FDG-PET scan images were displayed on coronal, transaxial, and sagittal planes and with rotating 3-D images. They were reviewed by 2 independent nuclear physicians (AC, Y-JC) who were blinded to the clinical disease activity corresponding to each scan. In cases of disagreement, the final interpretation was determined by consensus between the 2 nuclear physicians after an additional review. Visual analysis was performed on 11 vascular regions: ascending aorta, aortic arch, right innominate artery, right subclavian artery, right common carotid artery, left common carotid artery, left subclavian artery, descending thoracic aorta, abdominal aorta, right common iliac artery, and left common iliac artery.

We used 2 parameters to measure ^{18}F-FDG uptake values, visual grade and standard uptake value intensity. Visual grade is a semiquantitative measurement of ^{18}F-FDG activity, where 0 = no vascular uptake, 1 = vascular uptake less than liver uptake, 2 = vascular uptake similar to liver uptake, and 3 = vascular uptake greater than liver uptake. Active vascular ^{18}F-FDG uptake was defined as grade $\geq$2. For quantitative measurement of ^{18}F-FDG uptake, we obtained the standard uptake value, defined as the ratio of ^{18}F-FDG activity to the injected ^{18}F-FDG activity divided by the body mass index, from the region of interest (ROI) of each vascular region. In order to minimize the effect of time from injection to acquisition and to minimize the effect of blood glucose levels, we divided the standard uptake value of a vascular ROI with the maximal standard uptake value of the liver and named this value "standard uptake value intensity." For the selection of a representative value of the ^{18}F-FDG uptake of an FDG-PET scan, we selected 1 vascular ROI with the most intense ^{18}F-FDG uptake and measured it using both semiquantitative (visual grade) and quantitative (standard uptake value intensity) methods.

Assessment of clinical disease activity. When performing FDG-PET scans, we assessed the clinical disease activity in each patient on the basis of the National Institutes of Health (NIH) criteria for active disease in TA (1). TA was considered to be active when the patient experienced new development or worsening of $\geq$2 of the following: 1) systemic features (such as fever or musculoskeletal features) with no other cause identified, 2) elevated erythrocyte sedimentation rate (ESR), 3) features of vascular ischemia or inflammation, such as claudication, diminished or absent pulses, bruit, vascular pain (carotodynia), and asymmetric blood pressure in the upper or lower limbs (or both), and 4) typical angiographic features. Due to heterogeneity in the angiographic modalities, the definition of worsening of angiographic features was confined to the worsening of luminal changes in the affected vessel. The median duration between previous clinical evaluation and evaluation

Table 1. Baseline values of clinical disease activity, laboratory markers, and ^{18}F-FDG uptake*

Patient/age/sex	ESR, mm/hour	CRP, mg/dl	Clinical disease activity	PET disease activity†	Visual grade‡	SUV intensity§	Lesions with active ^{18}F-FDG uptake¶
1/37/F	29	NA	Yes	Yes	3	1.25	1–3, 5, 8–10
2/38/F	26	0.41	Yes	Yes	3	1.00	1, 2, 4–11
3/42/F	70	5.38	Yes	Yes	2	1.01	1
4/33/F	50	4.91	Yes	Yes	3	1.41	1–11
5/41/F	45	1.81	Yes	Yes	3	1.78	1, 3–6, 8–11
6/45/F	29	0.43	Yes	Yes	3	1.23	1–4, 6, 8
7/56/F	24	0.50	Yes	Yes	3	0.96	2, 3, 5, 6, 8
8/23/F	120	2.33	Yes	Yes	3	2.36	1–11
9/25/F	26	1.10	Yes	Yes	2	0.90	1, 2, 8
10/45/F	26	2.09	Yes	No	1	0.80	–
11/64/F	36	0.60	Yes	Yes	3	1.45	1, 8, 9
12/32/F	88	1.56	Yes	Yes	3	1.14	1–7, 9–11
13/23/F	44	0.34	Yes	Yes	3	1.07	1–3, 6, 7
14/39/F	30	0.38	Yes	No	1	1.10	–
15/58/F	10	0.20	Yes	No	1	0.78	–
16/53/F	8	0.94	Yes	No	1	0.86	–
17/28/F	2	0.10	Yes	Yes	2	0.96	1
18/67/M	22	0.17	Yes	No	1	0.79	–
19/40/M	64	1.33	Yes	Yes	3	0.72	1–6, 8–11
20/57/F	19	0.20	Yes	No	1	0.71	–
21/38/F	44	0.12	Yes	Yes	2	0.94	8
22/48/F	36	0.10	Yes	Yes	3	1.47	1, 2, 6, 8
23/43/F	17	0.49	Yes	Yes	3	1.73	1, 4, 5, 8, 9, 11
24/29/F	38	0.49	Yes	Yes	2	0.91	1, 2, 4, 5, 8–11
25/49/F	20	0.10	No	No	1	0.78	–
26/55/F	14	0.14	No	No	1	0.78	–
27/55/F	44	0.18	No	Yes	2	0.88	5
28/59/F	4	0.10	No	No	1	0.56	–
29/50/F	39	0.19	No	No	1	0.8	–
30/49/F	26	0.10	No	No	1	0.78	–
31/44/M	2	0.13	No	Yes	2	0.80	1, 2
32/26/F	61	2.41	No	No	1	0.74	–
33/52/F	23	0.27	No	Yes	2	0.95	1, 2, 8
34/41/F	48	0.14	No	No	1	0.84	–
35/48/F	47	0.725	No	No	1	0.73	–
36/26/M	4	0.21	No	No	1	0.82	–
37/45/F	14	0.10	No	Yes	2	0.83	1
38/36/F	12	0.21	No	Yes	2	0.71	1, 2, 6, 8

* ^{18}F-FDG = ^{18}F-fluorodeoxyglucose; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; NA = not available.
† Disease activity of Takayasu arteritis judged by ^{18}F-fluorodeoxyglucose–positron emission tomography (FDG-PET), where an FDG-PET scan shows at least 1 instance of active vascular ^{18}F-FDG uptake (visual grade ≥2).
‡ Semiquantitative measure of ^{18}F-FDG uptake, where 0 = no vascular uptake, 1 = vascular uptake less than liver uptake, 2 = vascular uptake similar to liver uptake, and 3 = vascular uptake greater than liver uptake. The visual grade of a vascular region of interest (ROI) with maximal ^{18}F-FDG uptake was selected.
§ Standard uptake value (SUV) intensity, defined as the ratio of maximal standard uptake value of a vascular ROI to the maximal standard uptake value of liver at the 1 vascular ROI with the most intense ^{18}F-FDG uptake.
¶ Vascular regions with visual grade values ≥2: 1 = ascending aorta, 2 = aortic arch, 3 = right innominate artery, 4 = right subclavian artery, 5 = right common carotid artery, 6 = left common carotid artery, 7 = left subclavian artery, 8 = descending thoracic aorta, 9 = abdominal aorta, 10 = right common iliac artery, 11 = left common iliac artery.

at the time of FDG-PET scanning was 3 months (range 1–5 months). Patients with inactive disease were defined as those who did not meet the NIH criteria for active TA.

Markers of inflammation. ESRs and C-reactive protein (CRP) levels were measured when FDG-PET was performed. ESR was measured by the modified Westergren method, and CRP level was measured by nephelometry (IMMAGE; Beckman Coulter). The normal range of ESR was defined as 0–15 mm/hour for male patients and 0–20 mm/hour for female patients. Increased CRP level was defined as a value >0.8 mg/dl.

Statistical analysis. We used SPSS software, version 15.0. A weighted kappa statistic was used to assess the degree of agreement between the 2 nuclear physicians. The Mann-Whitney U test was used to compare continuous variables in the groups with clinically active and inactive disease. The chi-square test was used to assess the association between clinical disease activity and disease activity judged by FDG-

Table 2. Comparison of ^{18}F-FDG uptake levels between patients with clinically active disease and those with clinically inactive disease*

	Clinically active disease (n = 24)	Clinically inactive disease (n = 14)	*P*
Age, mean ± SD years	41.7 ± 12.7	45.3 ± 10.1	NS
Female, no. (%)	22 (91.7)	12 (85.7)	NS
Glucose, mean ± SD mg/dl	93.5 ± 14.1	92.7 ± 10.1	NS
Visual grade, median (range)	2.5 (1–3)	1 (1–2)	0.001
SUV intensity, median (range)	1.01 (0.71–2.36)	0.79 (0.56–0.95)	<0.001
Vascular lesions with active ^{18}F-FDG uptake, median (range) no.	4.5 (0–11)	1.72 (0–4)	0.003

* NS = not significant (see Table 1 for other definitions).

PET. The association between ^{18}F-FDG uptake and ESR and CRP level was assessed by Kruskal-Wallis test and Spearman's correlation in the case of visual grade and standard uptake value intensity, respectively.

RESULTS

Baseline patient characteristics. A total of 38 patients were reviewed; 34 of them were female (89.5%). Their mean ± SD age was 43.0 ± 11.8 years. At the time of diagnosis, these patients' angiographic abnormalities were revealed by digital subtraction angiography in 9 patients, CT angiography in 20, and MR angiography in 9. Followup imaging with the same modality used at the time of diagnosis was performed in 28 patients 2 months (range 0.5–7 months) before baseline FDG-PET scanning. The median ESR value was 27.5 mm/hour (range 2–120) and the median CRP value was 0.26 mg/dl (range 0.1–5.38). Fifteen patients (39.5%) had discrepancies between ESR and CRP values. Twenty-four patients (63.2%) had clinically active disease. Among these 24 patients, the numbers fulfilling each NIH subcriterion were 22 for increased ESR (91.7%), 8 for angiographic features (33.3%), 7 for symptoms of vascular ischemia or inflammation (29.2%), and 5 for systemic features (20.8%). Twenty patients (83.3%) fulfilled 2 subcriteria, and the other 4 patients (16.7%) fulfilled 3 subcriteria.

Analysis of the baseline FDG-PET scans. Thirty-eight patients (4 males and 34 females) underwent 53 FDG-PET scans. Among these patients, 14 were receiving immunosuppressive drugs at the time of baseline FDG-PET scanning. Among the 38 baseline FDG-PET scans, 23 scans (60.5%) showed active vascular ^{18}F-FDG uptake (visual grade ≥2) in at least 1 vascular region. A mean ± SD 5.5 ± 3.15 regions had active vascular ^{18}F-FDG uptake. The ascending aorta (20 of 38 scans, 52.6%) and descending thoracic aorta (16 of 38 scans, 42.1%) were most commonly affected. Table 1 lists the baseline values of clinical disease activity, laboratory markers, and ^{18}F-FDG uptake of each patient. The weighted kappa score of interobserver agreement for the semiquantitative classification was very good (κ = 0.917).

Association with clinical disease activity. FDG-PET correctly identified 18 of 24 patients with clinically active disease (75%) and 9 of 14 patients with clinically inactive disease (64.3%). There was a significant association between clinical disease activity and disease activity judged by FDG-PET (P = 0.008). There were 6 false-negative scan results and 5 false-positive scan results. For clinically active disease, FDG-PET scans showed a sensitivity of 75%, a specificity of 64.3%, a positive predictive value (PPV) of 78.3%, and a negative predictive value of 60%. Median (range) visual grade (2.5 [1–3] versus 1 [1–2]; P = 0.001), standard uptake value intensity (1.01 [0.71–2.36] versus 0.79 [0.56–0.95]; $P < 0.001$), and number of vascular lesions with active ^{18}F-FDG uptake (4.5 [0–11] versus 1.72 [0–4]; P = 0.003) were significantly higher in patients with clinically active disease than in those without (Table 2).

Association with laboratory markers. Visual grade was significantly associated with the ESR (P = 0.041) and showed a trend toward association with the level of CRP (P = 0.053). Standard uptake value intensity was also significantly correlated with the ESR (r = 0.360, P = 0.026) and CRP level (r = 0.355, P = 0.031). The number of vascular lesions with active ^{18}F-FDG uptake was associated with the ESR (r = 0.511, P = 0.017) and CRP level (r = 0.426, P = 0.009).

Analysis of followup FDG-PET scans. Thirteen patients underwent 15 followup FDG-PET scans. Followup FDG-PET scans were performed to evaluate responses to immunosuppressive treatment. At baseline, 9 patients (patients 1–9) had clinically active disease and had at least 1 active ^{18}F-FDG uptake lesion (visual grade

Table 3. Results of followup FDG-PET scans*

Patient/age/sex, visit†	Elapsed time from baseline, months	Clinical disease activity	ESR, mm/hour	CRP, mg/dl	Visual grade‡	SUV intensity§	Lesions with active ^{18}F-FDG uptake¶	Treatment
1/37/F								
1	–	Yes	29	NA	3	1.25	1–3, 5, 8–11	MTX 10 mg + Pred. 60 mg
2	3	No	4	NA	2	0.97	1–6, 8	MTX 15 mg + Pred. 15 mg
2/38/F								
1	–	Yes	26	0.41	3	1.0	1, 2, 4–11	MTX 10 mg + Pred. 60 mg
2	7	No	38	0.39	2	0.72	5, 8, 9	MTX 15 mg + Pred. 15 mg
3/42/F								
1	–	Yes	70	5.38	2	1.01	1	MTX 10 mg + Pred. 60 mg
2	3	No	7	0.19	1	0.60	–	MTX 15 mg + Pred. 10 mg
4/33/F								
1	–	Yes	50	4.91	3	1.41	1–11	MTX 10 mg + Pred. 30 mg
2	1	No	2	0.1	2	0.67	1–2	MTX 15 mg + Pred. 20 mg
5/41/F								
1	–	Yes	45	1.81	3	1.78	1, 3–6, 8–11	MTX 10 mg + Pred. 60 mg
2	2	No	5	0.44	2	0.77	3, 8	MTX 15 mg + Pred. 20 mg
6/45/F								
1	–	Yes	29	0.43	3	1.23	1–4, 6, 8	MTX 10 mg + Pred. 60 mg
2	4	No	15	0.26	1	0.75	–	MTX 15 mg + Pred. 10 mg
7/56/F								
1	–	Yes	24	0.5	3	0.96	2, 3, 5, 6, 8	MTX 10 mg + Pred. 40 mg
2	5	No	12	0.29	2	0.83	5, 6, 8	MTX 15 mg + Pred. 10 mg
8/23/F								
1	–	Yes	120	2.33	3	2.36	1–11	MTX 10 mg + Pred. 60 mg
2	8	No	15	0.44	2	1.0	4, 5, 8	MTX 15 mg + Pred. 15 mg
3	33	Yes	98	1.91	3	1.33	1–9	MTX 15 mg + Pred. 60 mg
9/25/F								
1	–	Yes	26	1.1	2	0.90	1, 2, 8	Pred. 30 mg
2	3	Yes	8	0.46	3	1.01	1, 2, 4, 5, 8–11	MTX 10 mg + Pred. 30 mg
3	10	Yes	18	0.56	2	0.98	1, 2, 8	MTX 15 mg + Pred. 30 mg
35/48/F								
1	–	No	47	0.725	1	0.73	–	Pred. 30 mg
2	4	No	14	0.62	1	0.65	–	Pred. 10 mg
36/26/M								
1	–	No	4	0.21	1	0.82	–	MTX 7.5 mg + Pred. 20 mg
2	6	No	2	0.1	1	0.63	–	MTX 10 mg
37/45/F								
1	–	No	14	0.10	2	0.83	1	Pred. 20 mg
2	3	No	3	0.10	2	0.75	1	Pred. 10 mg
38/36/F								
1	–	No	12	0.21	2	0.71	1, 2, 6, 8	MTX 7.5 mg + Pred. 20 mg
2	10	Yes	41	0.70	3	1.12	1, 2, 6, 8	MTX 12.5 mg + Pred. 30 mg

* MTX = methotrexate; Pred. = prednisolone (see Table 1 for other definitions).
† Baseline visit is visit 1.
‡ Semiquantitative measure of ^{18}F-FDG uptake, where 0 = no vascular uptake, 1 = vascular uptake less than liver uptake, 2 = vascular uptake similar to liver uptake, and 3 = vascular uptake greater than liver uptake. The visual grade of a vascular ROI with maximal ^{18}F-FDG uptake was selected.
§ Defined as the ratio of maximal standard uptake value of a vascular ROI to the maximal standard uptake value of liver at the 1 vascular ROI with the most intense ^{18}F-FDG uptake.
¶ Vascular regions with visual grade values ≥2: 1 = ascending aorta, 2 = aortic arch, 3 = right innominate artery, 4 = right subclavian artery, 5 = right common carotid artery, 6 = left common carotid artery, 7 = left subclavian artery, 8 = descending thoracic aorta, 9 = abdominal aorta, 10 = right common iliac artery, 11 = left common iliac artery.

≥2) on their FDG-PET scans. These patients received moderate-to-high doses of prednisolone with methotrexate. The other 4 patients (patients 35–38) had clinically inactive disease according to the NIH criteria at baseline; however, immunosuppressive drugs including prednisolone and/or methotrexate were given to all 4 patients because two of them (patients 35 and 36) had mild ^{18}F-FDG uptake and two (patients 37 and 38) had active vascular uptake on the FDG-PET scans, which suggested the presence of inflammation in the arterial walls.

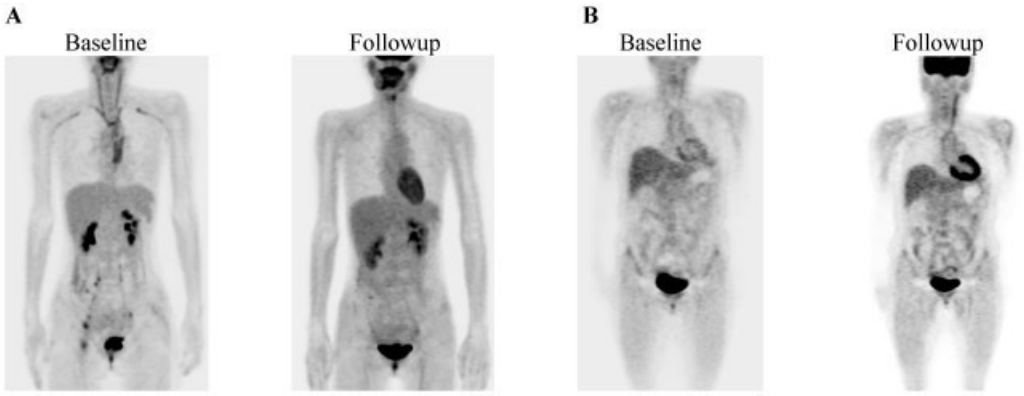

Figure 1. Changes in ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake on followup ^{18}F-fluorodeoxyglucose–positron emission tomography (FDG-PET) scans. **A,** FDG-PET scans of patient 8 at baseline and at followup. Patient 8 improved clinically after immunosuppressive treatment. Note the marked decrease in ^{18}F-FDG uptake in the ascending aorta and its branches as well as in the subclavian arteries on the followup FDG-PET scan performed 8 months after treatment. **B,** FDG-PET scans of patient 38 at baseline and at followup. Patient 38 experienced a disease flare. Note the increase in ^{18}F-FDG uptake in the left common carotid artery on the followup FDG-PET scan.

Followup FDG-PET scans were obtained 4.19 ± 2.5 months (mean ± SD) after the start of immunosuppressive treatment (Table 3).

Followup FDG-PET scans of patients with active disease at baseline. Eight of the 9 patients (patients 1–8) who had clinically active disease at baseline achieved inactive disease status in a median of 3.5 months (range 1–8 months). The decrease in visual grade ($P = 0.011$), standard uptake value intensity ($P = 0.008$), and extent of vascular uptake ($P = 0.028$) was statistically significant according to the Wilcoxon signed rank test on the followup FDG-PET scans in these 8 patients. Figure 1A shows the marked decrease in ^{18}F-FDG uptake on the followup FDG-PET scan after immunosuppressive treatment.

Patient 8 experienced a disease flare at the time of the third scan, when the visual grade, standard uptake value intensity, and extent of active ^{18}F-FDG uptake increased. Patient 9 continued to have clinically active disease despite treatment with prednisolone. In this case, the visual grade, standard uptake value intensity, and extent of active ^{18}F-FDG uptake had increased at the time of the second scan, but after more intensive immunosuppression these 3 parameters showed a decrease on the third scan (Tables 3 and 4).

Followup FDG-PET scans of patients with inactive disease at baseline. After immunosuppressive treatment, the extent of active vascular ^{18}F-FDG uptake and standard uptake value intensity decreased in 3 patients (patients 35–37). These 3 patients had inactive disease at followup, but patient 38 experienced a disease flare. The followup FDG-PET scan in this patient showed an increase in visual grade and standard uptake value intensity (Figure 1B and Tables 3 and 4).

Discrepancies between FDG-PET scans and clinical disease activity. The FDG-PET scan showed mild ^{18}F-FDG uptake (visual grade <2) in 6 of 24 patients with clinical disease activity. However, none of them showed an ^{18}F-FDG uptake of visual grade 0 in their vascular region. FDG-PET showed an increased ^{18}F-FDG uptake (visual grade ≥ 2) in 5 of the 14 patients without clinical disease activity. Two of these 5 patients underwent followup FDG-PET scans. One patient (patient 37) showed a decrease in ^{18}F-FDG uptake after immunosuppressive treatment, and the other (patient 38) showed a worsened feature on the followup scan despite immunosuppressive treatment. The latter patient turned out to have clinically active disease at the time of the followup scan (Table 3).

DISCUSSION

In this study of 53 FDG-PET scans of 38 patients, we found a significant association between ^{18}F-FDG uptake and clinical disease activity of TA defined by the NIH criteria. Similarly, ^{18}F-FDG uptake correlated well with commonly used surrogate markers such as the ESR and CRP level. Furthermore, our longitudinal analysis of the followup scans demonstrated that changes in FDG-PET scans in a given patient corresponded well to changes in clinical disease activity.

Our results are concordant with those of previous studies (9–14). Andrews et al reported that FDG-PET identified active vascular lesions in 5 of 6 patients with

Table 4. Comparison of visual grade scores between baseline and followup FDG-PET scans*

Patient/age/sex, visit†	Clinical disease activity	Localization‡								No. of lesions with active ^{18}F-FDG uptake
		Asc. A.	A. arch	Inn. A.	SCA (R/L)	CCA (R/L)	Desc. A.	Abd. A.	CIA (R/L)	
1/37/F										
1	Yes	2	3	3	1/0	3/0	3	2	2/2	7
2	No	2	2	2	1/0	2/2	2	1	1/1	5
2/38/F										
1	Yes	2	2	0	2/2	3/2	3	2	2/2	10
2	No	1	0	0	1/0	2/0	2	2	1/1	3
3/42/F										
1	Yes	2	1	1	1/1	1/1	1	1	1/1	1
2	No	1	0	0	1/0	1/0	1	1	1/1	0
4/33/F										
1	Yes	3	3	3	3/2	2/3	3	3	2/2	11
2	No	2	2	0	0/0	0/0	0	0	1/1	2
5/41/F										
1	Yes	3	0	3	2/0	3/2	3	2	2/2	9
2	No	1	0	2	1/0	1/0	2	1	1/1	2
6/45/F										
1	Yes	3	2	2	2/0	1/2	2	1	1/1	6
2	No	1	1	1	1/0	1/0	1	1	1/1	0
7/56/F										
1	Yes	1	2	2	1/0	2/3	2	1	1/1	5
2	No	1	1	0	1/0	2/2	2	1	1/1	3
8/23/F										
1	Yes	3	3	3	3/3	3/3	3	3	3/3	11
2	No	1	0	0	2/0	2/0	2	1	1/1	3
3	Yes	2	3	3	3/3	3/3	3	2	1/1	9
9/25/F										
1	Yes	2	2	0	1/0	1/0	2	1	2/2	3
2	Yes	2	2	0	2/0	2/0	3	2	0/0	8
3	Yes	2	2	0	1/0	1/0	2	1	0/0	3
35/48/F										
1	No	1	0	0	0/0	1/1	1	0	0/0	0
2	No	1	0	0	0/0	0/1	0	0	0/0	0
36/26/M										
1	No	0	0	0	0/0	1/0	0	1	1/1	0
2	No	0	0	0	0/0	1/0	0	0	1/1	0
37/45/F										
1	No	2	1	0	0/0	0/1	1	1	1/1	1
2	No	2	1	0	0/0	0/0	1	1	1/1	1
38/36/F										
1	No	2	2	0	1/0	1/2	2	1	–	4
2	Yes	2	2	0	1/0	1/3	2	1	–	4

* See Table 1 for other definitions.
† Baseline visit is visit 1.
‡ Asc. A. = ascending aorta; A. arch = aortic arch; Inn. A. = innominate artery; SCA = subclavian artery; R = right; L = left; CCA = common carotid artery; Desc. A. = descending aorta; Abd. A. = abdominal aorta; CIA = common iliac artery.

active TA, and that increased ^{18}F-FDG uptake at baseline decreased in all 4 patients who achieved remission after immunosuppressive treatment (9). Kobayashi et al reported no increased ^{18}F-FDG uptake in patients with inactive TA (11). Webb et al reported that FDG-PET identified 11 of 12 patients with active TA and all 6 patients with inactive TA (14). De Leeuw et al reported similar results in 5 patients with large-vessel vasculitis (10). Furthermore, we observed decreases in the extent of ^{18}F-FDG uptake as well as standard uptake value intensity in patients with clinically inactive disease at baseline, according to the NIH criteria, after immunosuppressive treatment.

Our results contrast with those of a study by Arnaud et al (8), which showed a lack of correlation between ^{18}F-FDG uptake, clinical disease activity, and levels of markers of inflammation. They pointed out that previous studies used various invalid criteria for active

TA and may therefore be biased. They depended exclusively on clinical symptoms without markers of inflammation when assessing clinical disease activity and reported that the FDG-PET scan had a sensitivity of 69.2% and a specificity of 33.3% for clinically active TA. However, among the 27 patients in their study who underwent FDG-PET scans that showed clinically inactive disease, 9 had either increased ESRs or increased CRP levels. Arnaud et al might have underestimated the disease activity in these patients.

Increased ^{18}F-FDG uptake was seen in 5 patients with clinically inactive disease. It is difficult to explain this discrepancy because histologic examination was not available in our study. It may reflect vascular remodeling or atheroma. Alternatively, it could reflect residual inflammation of the arterial wall identified in surgical specimens from patients with clinically inactive disease (1,2). Some of them showed a response to immunosuppressive treatment on the followup scan. Although increased ^{18}F-FDG uptake in patients with clinically inactive disease may reflect residual inflammation, the long-term implications of such findings and the value of changing therapy based on such results are not known.

In contrast, 6 patients with active disease did not show active ^{18}F-FDG uptake. None of them, however, showed an absence of ^{18}F-FDG uptake. They showed mild ^{18}F-FDG uptake in their vascular regions. This mild ^{18}F-FDG uptake may reveal inflammation of the arterial wall. Pathologic confirmation or followup of these mild ^{18}F-FDG uptake findings would be helpful in determining their clinical implications. Unfortunately, followup FDG-PET scan was not available in these patients.

We assessed ^{18}F-FDG uptake using various methods in order to measure it more accurately and comprehensively. The method of assessing ^{18}F-FDG uptake varied according to the study. Some studies used semiquantitative analysis comparing the ^{18}F-FDG uptake of a vascular ROI with that of the liver (9,10), while others quantified ^{18}F-FDG uptake using methods such as standard uptake value (11,13). We measured ^{18}F-FDG uptake using both semiquantitative (visual grade) and quantitative (standard uptake value intensity) methods and checked the number of vascular lesions with active ^{18}F-FDG uptake to quantify the extent of disease. We found a significant association between clinical disease activity and ^{18}F-FDG uptake, regardless of the way it was measured. We used standard uptake value intensity to quantitatively measure ^{18}F-FDG uptake. Standard uptake value may vary according to various factors including serum glucose level, uptake time, ROI geometry, and the like (20). To minimize the effects of various confounders, we adjusted the standard uptake value of an ROI in a vascular region with the maximal standard uptake value of the liver, which may reduce the effect of uptake time and serum glucose level.

Fourteen patients were receiving immunosuppressive drugs including glucocorticoids at the time of the baseline FDG-PET scan. Although acute hyperglycemia induced by glucocorticoids was reported to reduce ^{18}F-FDG uptake (21,22), there was no difference in blood glucose levels between patients with active disease and those with inactive disease on FDG-PET scans in our study. However, little is known about the effects of other immunosuppressive drugs on ^{18}F-FDG uptake, and we cannot completely exclude their potential effects.

Similar results were reported in patients with giant cell arteritis (GCA), another type of large-vessel vasculitis (23). Although FDG-PET could not reveal the inflammatory changes in cranial branches of arteries originating from the aortic arch due to their small diameter and superficial location, FDG-PET was valuable in detecting inflammatory changes in the large extracranial arteries in GCA (24,25). Thoracic vascular ^{18}F-FDG uptake showed a sensitivity of 56%, a specificity of 98%, and a PPV of 93% for the diagnosis of GCA and polymyalgia rheumatica (26). However, questions have been raised as to the role of FDG-PET in following up patients with GCA, as FDG-PET was unable to identify which patients would have relapse of their disease (27).

Assessment of the disease activity of TA is challenging. Clinical symptoms and laboratory markers for the assessment of disease activity of TA may not fully reflect the actual inflammation in the arterial wall (1). Imaging modalities such as CT, MRI, and ultrasonography may reveal inflammatory changes of the arterial wall, but they have several limitations in assessing the actual disease activity of TA (3). FDG-PET scanning is a functional imaging technique capable of quantifying the burden of inflammation, and several studies have shown that it correlates well with disease activity of TA. In our study, ^{18}F-FDG uptake in patients with active TA showed a significant response to immunosuppressive treatment. FDG-PET may have a role in the assessment of disease activity of TA, especially in patients in whom disease activity is unclear based on clinical symptoms and laboratory markers.

Our study has several limitations. Because our study was retrospective, it may have weaknesses such as a selection bias and incomplete or suboptimal data collection. However, our series consisted of consecutive patients who agreed to undergo a PET scan. Prospective

confirmation of our findings would be valuable. Second, we used the NIH criteria as a tool for assessing the disease activity of TA. Currently, there is no definitive gold standard for assessing disease activity in TA (28). Although it is worthwhile to note that these criteria have also been used in several other studies (9,29,30), they are, nonetheless, neither standardized nor validated as assessments of clinical disease activity in TA. Therefore, further research is needed to develop a validated set of outcome measures for use in clinical trials of TA (28). Third, not all the patients underwent regular angiographic assessment, which is a component of the NIH criteria for active disease in TA. In addition, concomitant angiography at times of FDG-PET scan was not available in this study. Finally, we were not able to perform followup FDG-PET scans in all the patients. Followup FDG-PET scans were performed only in patients who agreed to undergo followup imaging.

To the best of our knowledge, our study is the largest in terms of the number of patients (n = 38) and the number of FDG-PET scans (n = 53). Although previous studies suggested the usefulness of FDG-PET, they enrolled smaller numbers of patients to support the value of FDG-PET due to the rarity of the disease. We assessed the association between ^{18}F-FDG uptake, clinical disease activity, and markers of inflammation. Although our results alone may not be sufficient to suggest the superiority of FDG-PET over clinical disease activity and markers of inflammation, its substantial correlation with these existing variables gives support to the potential value of this noninvasive imaging modality in the diagnosis and management of TA. Of note is the difficulty in obtaining pathologic samples from TA patients, because TA involves large vessels. In this respect, a prospective followup study would be helpful to investigate the usefulness of FDG-PET for the assessment of disease activity in patients with TA.

In conclusion, our data suggest that ^{18}F-FDG uptake is associated with clinical disease activity and markers of inflammation, and that FDG-PET reflects changes in clinical disease activity in patients with TA. FDG-PET may be a useful tool for aiding in the assessment of disease activity in patients with TA.

ACKNOWLEDGMENT

We thank Professor Hyon K. Choi (Section of Rheumatology, Boston University, Boston, Massachusetts) for his valuable comments on the manuscript.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Y.-B. Park had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data. K.-H. Lee, Cho, Choi, S.-W. Lee, Ha, Jung, M.-C. Park, J.-D. Lee, S.-K. Lee, Y.-B. Park.

Analysis and interpretation of data. K.-H. Lee, Cho, M.-C. Park, S.-K. Lee, Y.-B. Park.

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