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^{68}Ga-FAPI PET/CT for Rheumatoid Arthritis: A Prospective Study

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Conflicts of interest are listed at the end of this article.

See also the editorial by Williams and Ahlman in this issue.

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Background: In rheumatoid arthritis (RA), fibroblast-like synoviocyte cells, which are involved in inflammation of the articular cartilage and bone, overexpress fibroblast activation protein (FAP). This is a feature that could be leveraged to improve imaging assessment of disease.

Purpose: To determine the performance of gallium 68 (^{68}Ga)-labeled FAP inhibitor (FAPI) in assessing joint disease activity of RA and to compare with fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) imaging.

Materials and Methods: Twenty participants with RA (15 women; mean age, 55 years ± 10 [SD]) were prospectively enrolled from September 2020 to December 2021 and underwent clinical and laboratory assessment of disease activity and dual-tracer PET/CT (^{68}Ga-FAPI and ^{18}F-FDG) imaging. Imaging-derived variables of PET joint count (the number of joints positive for RA at PET) and PET articular index (a sum of the points of the joints using a three-point scale) were correlated to clinical and laboratory variables of disease activity.

Results: The combined output of both PET/CT techniques helped detect 244 affected joints, all of which showed positive results at ^{68}Ga-FAPI PET/CT. However, fifteen of 244 (6.1%) FAPI-avid joints in six of 20 (30%) participants were not detected at ^{18}F-FDG PET/CT. The maximum standardized uptake value of the most affected joint in each participant was higher in ^{68}Ga-FAPI than in ^{18}F-FDG PET/CT (9.54 ± 4.92 vs 5.85 ± 2.81, respectively; $P = .001$). The maximum standardized uptake values of the joints at both ^{68}Ga-FAPI and ^{18}F-FDG PET/CT were positively correlated with laboratory evaluation of C-reactive protein levels ($r = 0.49$ [$P = .03$] and 0.54 [$P = .01$], respectively). The PET joint count and PET articular index scores at ^{68}Ga-FAPI PET/CT were also positively correlated with most clinical disease activity variables and radiographic progression of joint damage ($P < .05$).

Conclusion: In participants with rheumatoid arthritis who underwent gallium 68 fibroblast activation protein inhibitor PET/CT, the extent of joint involvement correlated with clinical and laboratory variables of disease activity and showed a greater amount and degree of affected joints than at fluorine 18 fluorodeoxyglucose PET/CT.

Clinical trial registration no. NCT 04514614

Supplemental material is available for this article.

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disorder that primarily involves synovial joints. The uncontrolled arthritis usually leads to the destruction of joints because of erosion of cartilage and bone and additionally causes joint deformities. Treatment strategies are directed toward the control of synovitis and prevention of joint injury. The general principles of treatment include early recognition and diagnosis of RA, early use of disease-modifying antirheumatic drugs, and efforts toward tight control with a treat-to-target strategy (1,2). Frequent assessment of disease activity, often occurring every 3 months, is essential to maintaining control of RA with appropriate antirheumatic drugs and anti-inflammatory therapies and results in improved functional outcomes (1–4). Clinical assessment of disease activity usually includes physical examination of the joints, acute-phase reactant levels, and patient reporting of disease activity and quality of life (5). However, physical examination and patient self-reporting may lack reproducibility in clinical practice (6). Instead, imaging can serve as a reliable, reproducible, and objective indicator of synovitis and disease activity.

Fibroblast-like synoviocyte cells have a central role in the pathogenesis of RA. These cells, located in the lining and sublining of the synovium, contribute to pannus formation and the destruction of articular cartilage and bone. Studies have demonstrated high expression of fibroblast

Abbreviations

DAS28 = disease activity score using 28 joint counts, FAP = fibroblast activation protein, FAPI = FAP inhibitor, FDG = fluorodeoxyglucose, RA = rheumatoid arthritis

Summary

PET/CT with gallium 68–labeled fibroblast activation protein inhibitor demonstrated increased uptake in the affected joints of participants with rheumatoid arthritis and correlated with clinical and laboratory disease markers.

Key Results

- In a prospective study of 20 participants with moderate to severe rheumatoid arthritis (RA) who underwent PET/CT with gallium 68 (^{68}Ga)-labeled fibroblast-activation protein inhibitor (FAPI), the number of joints positive for RA at PET and degree of uptake was correlated with clinical assessment and C-reactive protein levels ($P < .05$).
- The maximum standard uptake value of the most affected joint in each participant was higher with ^{68}Ga-FAPI than with ^{18}F fluorodeoxyglucose (9.54 vs 5.85, respectively; $P < .001$).

activation protein (FAP), a type II cell surface serine protease, in fibroblast-like synoviocytes in the synovial tissues of individuals with RA (7,8). This finding was confirmed in our previous unpublished work on FAP expression in RA, osteoarthritis, and healthy control participants (Fig S1). Preclinical studies using PET and SPECT with a radiolabeled anti-FAP antibody have also shown high tracer accumulation in inflamed joints in murine experimental models of RA (9–11). Recently, a study (12) showed depletion of FAP-expressing fibroblasts suppressed both inflammation and bone erosions in mouse models of persistent arthritis. In another study (13), ex vivo anti-FAP targeted photodynamic therapy was attempted in RA synovial explants, and the synovial tissues treated with FAP-targeted photodynamic therapy showed enhanced expression of markers of cell damage and death in the synovial lining layer. These studies confirm the role of FAP in synovitis and support the approach of FAP-targeted clinical imaging in participants with RA. The purpose of our study was to determine the performance of gallium 68 (^{68}Ga)-labeled FAP inhibitor (FAPI) in assessing joint disease activity of RA and to compare it with fluorine 18 (^{18}F) fluorodeoxyglucose (FDG) imaging.

Materials and Methods

Study Design and Participants

Our prospective cohort study evaluated the role of ^{68}Ga-FAPI PET/CT in the treatment of RA. Our study was approved by the institutional review board of Peking Union Medical College Hospital (*Clinicaltrials.gov*: NCT04514614). A total of 20 participants with RA fulfilling the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for RA (14) were consecutively recruited in the Department of Rheumatology and Clinical Immunology of Peking Union Medical College Hospital between September 2020 and December 2021. Written informed consent was obtained from each patient. At enrollment, the disease activity of RA was assessed clinically by two experienced rheumatologists

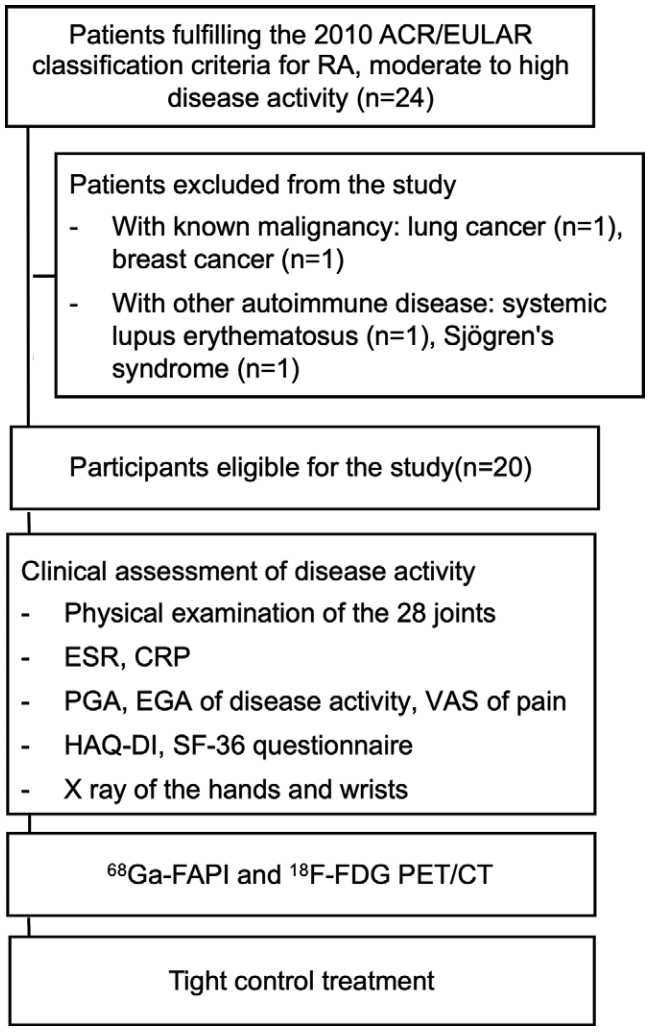

Figure 1: Flowchart of patient enrollment and study profile. ACR = American College of Rheumatology, CRP = C-reactive protein, EGA = evaluator global assessment, ESR = erythrocyte sedimentation rate, EULAR = European League Against Rheumatism, FAPI = fibroblast activation protein inhibitor, FDG = fluorodeoxyglucose, HAQ-DI = health assessment questionnaire disability index, PGA = patient global assessment of disease activity, RA = rheumatoid arthritis, SF-36 = Medical Outcomes Study short form-36, VAS = visual analog scale.

(H.Y. and M.L.). Participants with moderate to high disease activity according to clinical disease activity index were enrolled. We excluded participants with a known malignancy or other autoimmune disorder. Participants underwent ^{68}Ga-FAPI PET/CT and ^{18}F-FDG PET/CT for comparison purposes because ^{18}F-FDG is a well-established agent for depiction of inflammation. The order of the dual-tracer PET/CT scans was randomized, and scans were completed within 1 week following enrollment. Radiography in the hands and wrists was performed at baseline. After imaging, all participants underwent treatment for RA. A flow diagram of patient enrollment and study profile is shown in Figure 1.

Clinical Assessment of Disease Activity

The core variables of disease activity included the following: physical examination of the joints, including tender joint count (pain on pressure or motion) and swollen joint count (soft-tissue swelling and effusion) using 28 joint counts (shoulder, elbow,

wrist, metacarpophalangeal joint, proximal interphalangeal joint, knee) (5); laboratory measures of acute-phase response via erythrocyte sedimentation rate (millimeters per hour) and C-reactive protein (milligrams per liter); patient assessment of pain, patient global assessment, and evaluator global assessment of disease activity with visual analog scales; and patient self-report questionnaire of physical function assessment including health assessment questionnaire disability index and the Medical Outcomes Study short form–36. The composite indexes for disease activity assessment were calculated, which included clinical disease activity index (a numerical sum of tender joint count, swollen joint count, patient global assessment, and evaluator global assessment), simplified disease activity index (the sum of clinical disease activity index and C-reactive protein level), and disease activity score using 28-joint counts (DAS28) with either erythrocyte sedimentation rate or C-reactive protein (5).

PET/CT Imaging

The 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, or DOTA, FAPI-04 peptide was used (CSBio). The radiolabeling of ^{68}Ga-FAPI was performed manually before injection following a procedure by Luo et al (15). ^{18}F-FDG was synthesized in-house with an 11-MeV cyclotron (CTI RDS 111; Siemens). The PET scans were obtained by using dedicated PET/CT scanners (Biograph 64 Truepoint TrueV, Siemens; Polestar m660, SinoUnion). For ^{18}F-FDG PET/CT, participants fasted for longer than 6 hours, and blood glucose levels were monitored (4.5–7.8 mmol/L) before an injection of ^{18}F-FDG (5.55 MBq per kilogram of body weight). The PET/CT images (2 minutes per bed) were acquired with an uptake time of 76.5 minutes ± 14.8 (SD). For ^{68}Ga-FAPI PET/CT, imaging was performed (2 minutes per bed) with an uptake time of 51.5 minutes ± 13.6 after an injection of 104.3 MBq ± 31.0 ^{68}Ga-FAPI. PET/CT was performed from the tip of the skull to the knee. The acquired data were reconstructed using the ordered subset expectation maximization method.

Image Interpretation

The PET/CT images were transferred to a Siemens Multimodality workstation. Two nuclear medicine physicians (Y.L., with >10 years of experience in PET/CT and 3 years of experience in general radiology training, and Q.P., with >10 years of experience in PET/CT) worked together to assess the PET/CT images in a random order. Readers were blinded to clinical data except RA diagnosis and performed a consensus image interpretation. Clinically, joint involvement by RA refers to tender or swollen joints at physical examination performed by senior rheumatologists or evidence of synovitis at imaging. At PET/CT, a joint positive for RA was defined by increased articular radioactivity compared with the background uptake. The joints positive for RA detected at either ^{18}F-FDG or ^{68}Ga-FAPI PET/CT were analyzed joint-by-joint and compared with the tender and swollen joint determined by physical examination. Sites and uptake intensity of joints were recorded using a three-point scale (considering blood pool and either liver for ^{18}F-FDG or gluteal muscle for ^{68}Ga-FAPI), as follows: 0 points: no observed uptake; 1 point: joint uptake higher than or equal to blood pool but lower than or equal to liver and/or muscle uptake; 2 points: joint uptake higher than liver and/or muscle uptake but lower than or equal to two times the liver and/or muscle uptake; 3 points: joint uptake greater than two times the liver and/or muscle uptake. The number of joints positive for RA at PET was recorded as PET joint count (16), which was regarded as a main outcome of our study. A PET articular index was calculated as a sum of the points of the joints using the 28-joint counts, which was regarded as an exploratory outcome. The standardized uptake value of each joint was regarded as a secondary outcome and was measured by the same nuclear medicine physicians who were readers by using the volume-of-interest method with a unified standard approach. Spherical regions of interest were placed in the ascending aorta (for blood pool, 1-cm diameter), right hepatic lobe (for liver, 3-cm diameter), and gluteus maximus (for muscle, 1-cm diameter) for background measurement. Radiography was interpreted by a certified radiologist (Y.L.).

Statistical Analysis

Statistical analyses were performed (Y.L.) with software (Medcalc version 19.6.4; Medcalc Software). Comparison of the maximum standardized uptake value of the joints at ^{18}F-FDG or ^{68}Ga-FAPI PET/CT was performed using a paired *t* test for data with normal distribution and paired samples Wilcoxon test for skewed data (Shapiro-Wilk test for normality). The McNemar test was used to statistically compare the detection rate of ^{18}F-FDG and ^{68}Ga-FAPI PET/CT. Correlation analyses with Pearson correlation coefficients (for data with normal distribution) or Spearman rank correlation coefficients (for skewed data) were conducted. For correction of multiple comparisons, Benjamini-Hochberg method was performed to control the rates of false-positive findings. A *P* value less than .05 was considered to indicate statistical significance. The study was initially powered for at least 19 participants with the following parameters: expected correlation coefficient, 0.6; significance, .05; power, 0.8.

Results

Clinical Characteristics

Twenty participants with RA (five men and 15 women; 55 years ± 10) were enrolled in this prospective study. Nine participants had recent-onset RA that had not been treated previously, and 11 participants had a history of RA with recurrent or active disease at enrollment. The participants had a median disease duration of 48 months (range, 1–372 months). They were assessed to have moderate-to-high disease activity using clinical disease activity index (>10), simplified disease activity index (>11), and DAS28 (>3.2). The clinical characteristics are summarized in Table 1.

Detection of Affected Joints at ^{68}Ga-FAPI and ^{18}F-FDG PET/CT

^{68}Ga-FAPI and ^{18}F-FDG PET/CT images were visually positive for presence of RA joints in all participants (Figs 2, 3). A total of 244 joints positive for RA (using 28-joint counts) were detected at PET/CT, with a median PET joint count of 10 (range, 1–28) in each participant. The 244 joints had positive results at ^{68}Ga-FAPI PET/CT, whereas 15 of 244 (6.1%) FAPI-avid joints in six of 20 (30%) participants were not detected at ^{18}F-FDG PET/

Table 1: Clinical Characteristics of Enrolled Participants with Rheumatoid Arthritis (*n* = 20)

Characteristic	Value
Age (y)	55 ± 10 (25–73)
Sex	
No. of male participants	5
No. of female participants	15
Erythrocyte sedimentation rate (mm/h)	58.9 ± 27.9
CRP (mg/L)	42.4 ± 45.7
Rheumatoid factor (U/mL)	178.5 ± 157.9
No. of patients positive for anti-CCP antibody*	18 (90.0%)
Tender joint counts†	10.5 ± 4.6
Swollen joint counts†	8.9 ± 4.5
VAS of pain	6.4 ± 1.4
PGA of disease activity	6.2 ± 1.2
EGA of disease activity	6.9 ± 1.0
HAQ-DI‡	1.7 ± 0.7
SF-36‡	46.4 ± 9.1
CDAI†	32.5 ± 9.3
SDAI†	36.7 ± 12.2
DAS28-ESR†	6.2 ± 0.9
DAS28-CRP†	5.7 ± 1.2
Radiography‡§	
Stage I	5 (25)
Stage II	1 (5)
Stage III	10 (50)
Stage IV	2 (10)

Note.—Unless otherwise indicated, data are mean ± SD with range in parentheses. CCP = cyclic citrullinated peptide, CDAI = clinical disease activity index, CRP = C-reactive protein, DAS28 = disease activity score with 28-joint counts, EGA = evaluator global assessment, ESR = erythrocyte sedimentation rate, HAQ-DI = health assessment questionnaire disability index, PGA = patient global assessment, SDAI = simplified disease activity index, SF-36 = Medical Outcomes Study short form–36, VAS = visual analog scale.

* Data in parentheses are percentage.

† Assessed using 28-joint counts.

‡ Data not available in some participants.

§ Radiographic progression of joint damage was staged as follows: stage I, periarticular osteoporosis without destructive changes; stage II, joint space narrowing; stage III, cartilage and bone destruction; stage IV, joint deformity with fibrous or bony ankylosis. Data are number of patients; data in parentheses are percentages.

CT. A comparison of uptake in joints showed that the maximum standardized uptake value of the most affected joint in each participant was higher in ^{68}Ga-FAPI than in ^{18}F-FDG PET/CT (maximum standardized uptake value, 9.54 ± 4.92 vs 5.85 ± 2.81, respectively; $P < .001$), and the maximum standardized uptake value of the joints in both ^{68}Ga-FAPI and ^{18}F-FDG PET/CT were positively correlated with C-reactive protein levels (r = 0.49 [$P = .03$] and 0.54 [$P = .01$], respectively).

At clinical assessment, 237 tender or swollen joints (using 28-joint counts) were determined with a physical examination. When combining physical examination and PET/CT, a total of 314 joints were found to be involved. Among them, 167 joints had positive findings at both physical examination and ^{68}Ga-FAPI PET/CT, whereas 77 joints were not tender or swollen at clinical assessment, but positive findings were detected at ^{68}Ga-FAPI PET/CT. Seventy tender or swollen joints did not show uptake of ^{18}F-FDG or ^{68}Ga-FAPI. The positivity rate for detecting involved joints was 75.5% (237 of 314) for physical examination and 77.7% (244 of 314) for ^{68}Ga-FAPI PET/CT. The rate of RA joints detected at both physical examination and ^{68}Ga-FAPI PET/CT was 53.2% (167 of 314). The positivity rate of detecting involved joints at ^{68}Ga-FAPI PET/CT was higher than that at ^{18}F-FDG PET/CT (77.7% vs 72.9%, respectively; $P < .001$).

Other than the 28-joint area, 39 additional joints positive for RA in nine participants were also detected at both ^{68}Ga-FAPI and ^{18}F-FDG PET/CT, including the temporomandibular joint (n = 9), distal interphalangeal joint (n = 11), atlantoaxial joint (n = 3), hip (n = 7), sternoclavicular joint (n = 6), cricoarytenoid joint (n = 1), acromioclavicular joint (n = 1), and sacroiliac joint (n = 1). The participants with concurrent involvement in these joints had higher disease activity (DAS28–erythrocyte sedimentation rate, 6.66 ± 0.74 vs 5.81 ± 0.90, respectively [$P = .04$]; DAS28–C-reactive protein, 6.32 ± 1.28 vs 5.11 ± 1.00, respectively [$P = .03$]), higher levels of erythrocyte sedimentation rate (80.2 ± 14.2 vs 41.4 ± 25.6, respectively; $P < .001$) and C-reactive protein (7.07 ± 5.57 vs 1.94 ± 1.95, respectively; $P = .01$), and higher PET articular index than in participants with arthritis in the 28-joint area alone (33.2 ± 23.5 vs 14.5 ± 11.6, respectively; $P = .04$). Uptake at ^{68}Ga-FAPI and ^{18}F-FDG PET/CT in nonarticular tissues is discussed in Appendix S1.

Correlations of Clinical Assessments of Disease Activity and PET/CT

Quantitative PET/CT variables including PET joint count and PET articular index at both ^{68}Ga-FAPI and ^{18}F-FDG PET/CT and clinical assessment of disease activity analysis results are in Table 2. The PET joint count and PET articular index at ^{68}Ga-FAPI PET/CT were positively correlated with the tender or swollen joint counts, erythrocyte sedimentation rate, C-reactive protein, health assessment questionnaire disability index, simplified disease activity index, DAS28 erythrocyte sedimentation rate, DAS28 C-reactive protein, and radiographic staging. With ^{68}Ga-FAPI PET/CT, the PET joint count was negatively correlated with Medical Outcomes Study Short Form 36 score.

Follow-up PET/CT after Treatment

Three participants underwent follow-up ^{68}Ga-FAPI and ^{18}F-FDG PET/CT after 6–10 months of treatment. According to the American College of Rheumatology/European League Against Rheumatism response criteria (17–20), two participants with a good response and remission of the disease showed reduced uptake of ^{68}Ga-FAPI and ^{18}F-FDG in their joints. Reduced uptake was also observed in the hypermetabolic nodes near the affected major joints, and the ^{68}Ga-FAPI uptake markedly decreased in the salivary gland in one participant. A participant who had persistent active disease (high disease activity at baseline, moderate disease activity at follow-up) showed a reduction of uptake in some arthritic joints, but there was still active uptake of ^{68}Ga-

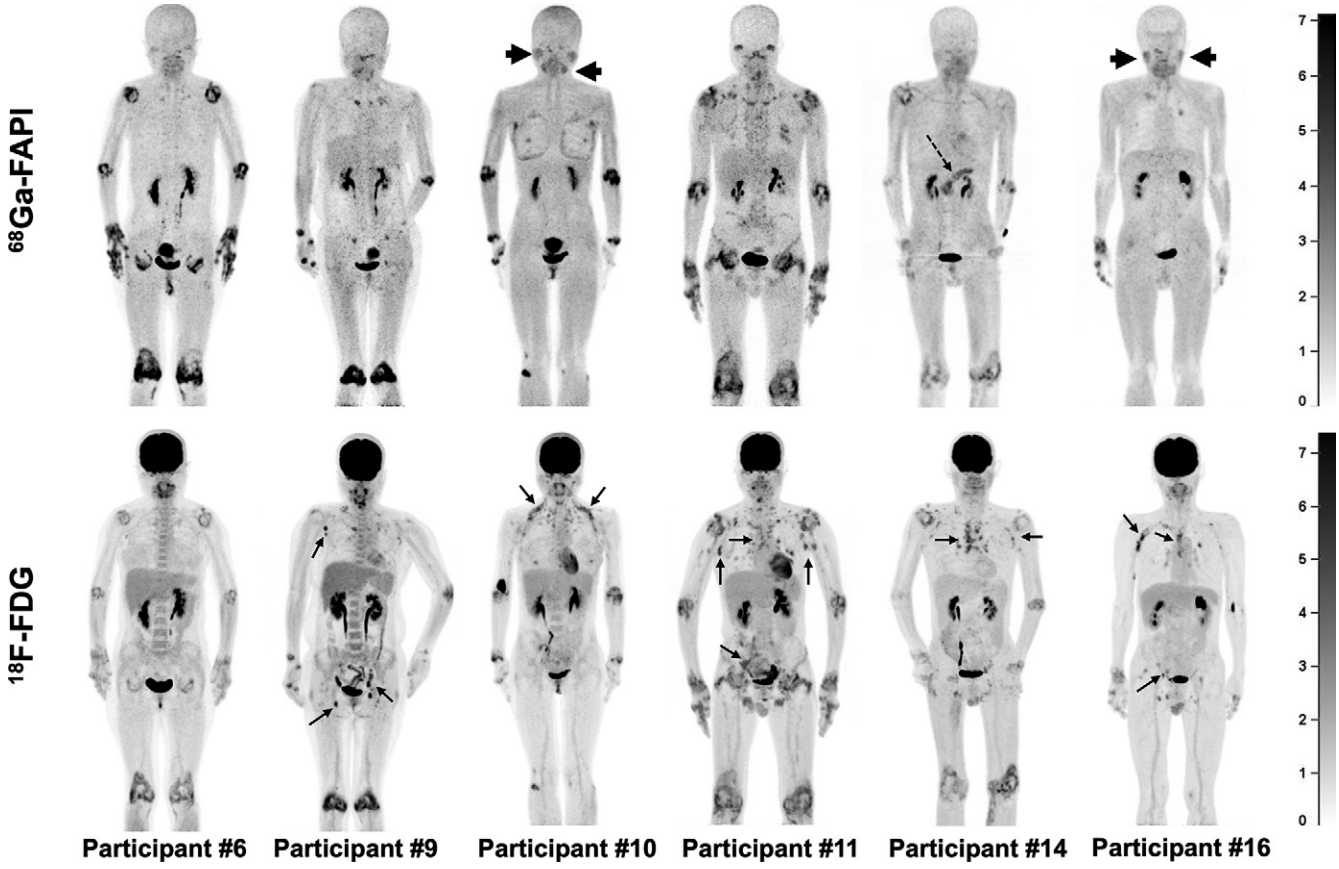

Figure 2: Individual comparison of six participants with rheumatoid arthritis undergoing gallium 68 (^{68}Ga)-labeled fibroblast activation protein inhibitor (FAPI) and fluorine 18 (^{18}F)-labeled fluorodeoxyglucose (FDG) PET/CT. Moderate to intense uptake of both tracers in the arthritic joints is shown, and the uptake intensity of ^{68}Ga-FAPI is comparable to or higher than that of ^{18}F-FDG PET/CT. Hypermetabolic lymph nodes on ^{18}F-FDG PET/CT images do not show uptake of ^{68}Ga-FAPI (participant 9, 10, 11, 14, 16; arrows). ^{68}Ga-FAPI uptake in the salivary gland (participant 10, 16; short arrows) and pancreas (participant 14, dashed arrow) is shown.

FAPI and ^{18}F-FDG in three major joints 6 months after treatment (Fig 4). Clinical assessment of disease activity at baseline and posttreatment results are in Table 3.

Discussion

We found a higher positivity rate and higher uptake intensity of gallium 68 (^{68}Ga) fibroblast activation protein inhibitor (FAPI) in detecting affected joints in participants with rheumatoid arthritis (RA) compared with fluorine 18 (^{18}F) fluorodeoxyglucose (FDG; positivity rate, 77.7% [244 of 314] vs 72.9% [229 of 314], respectively [P < .001]; maximum standardized uptake value, 9.54 ± 4.92 vs 5.85 ± 2.81, respectively [P < .001]). The quantitative variables including PET joint count and PET articular index at ^{68}Ga-FAPI PET/CT were correlated with clinical disease activity measurements and radiographic progression of joint damage. In most cases, ^{18}F-FDG and ^{68}Ga-FAPI PET/CT were comparable in detecting joint involvement, but we noted that two participants had intense ^{68}Ga-FAPI uptake but less ^{18}F-FDG avidity in the affected joints (maximum standardized uptake value, ^{18}F-FDG vs ^{68}Ga-FAPI PET/CT: 18.0 vs 5.0 and 6.9 vs 1.8, respectively). This may have been because of the treatment effect from medications that the participants were administered. Before enrollment in this study, one participant had been treated with dexamethasone and the other with disease-modifying antirheumatic drugs etanercept and tocilizumab. ^{18}F-FDG uptake in sites of inflammation may be reduced after treatment with glucocorticoids, as previously reported in large vessel vasculitis (21). In addition, certain drugs used in RA such as tumor necrosis factor or interleukin-6 receptors and Janus kinase inhibitors may inhibit proinflammatory cytokines or related signal transduction pathways. Because ^{18}F-FDG uptake depends on the high glycolytic activity of inflammatory cells, this imaging agent may underestimate disease activity of RA in participants who underwent treatments capable of suppressing inflammation before undergoing imaging.

Of the total 314 joints detected at ^{18}F-FDG PET/CT, ^{68}Ga-FAPI PET/CT, or physical examination, 70 tender or swollen joints (70 of 314; 22.3%) showed no uptake of ^{18}F-FDG or ^{68}Ga-FAPI. The inflammatory destructive process leads to irreversible and cumulative damage of the joint. As structural damage progresses, the detection of change in disease activity at physical examination of tender and swollen joints becomes increasingly difficult because symptoms and signs may be caused either by active rheumatoid disease or as a result of mechanical and degenerative change (secondary osteoarthritis). We think this might be an explanation for the negative findings at PET/CT in these joints, and we further question whether PET/CT (particularly ^{68}Ga-FAPI) can help distinguish the actual disease activity from irreversible joint damage.

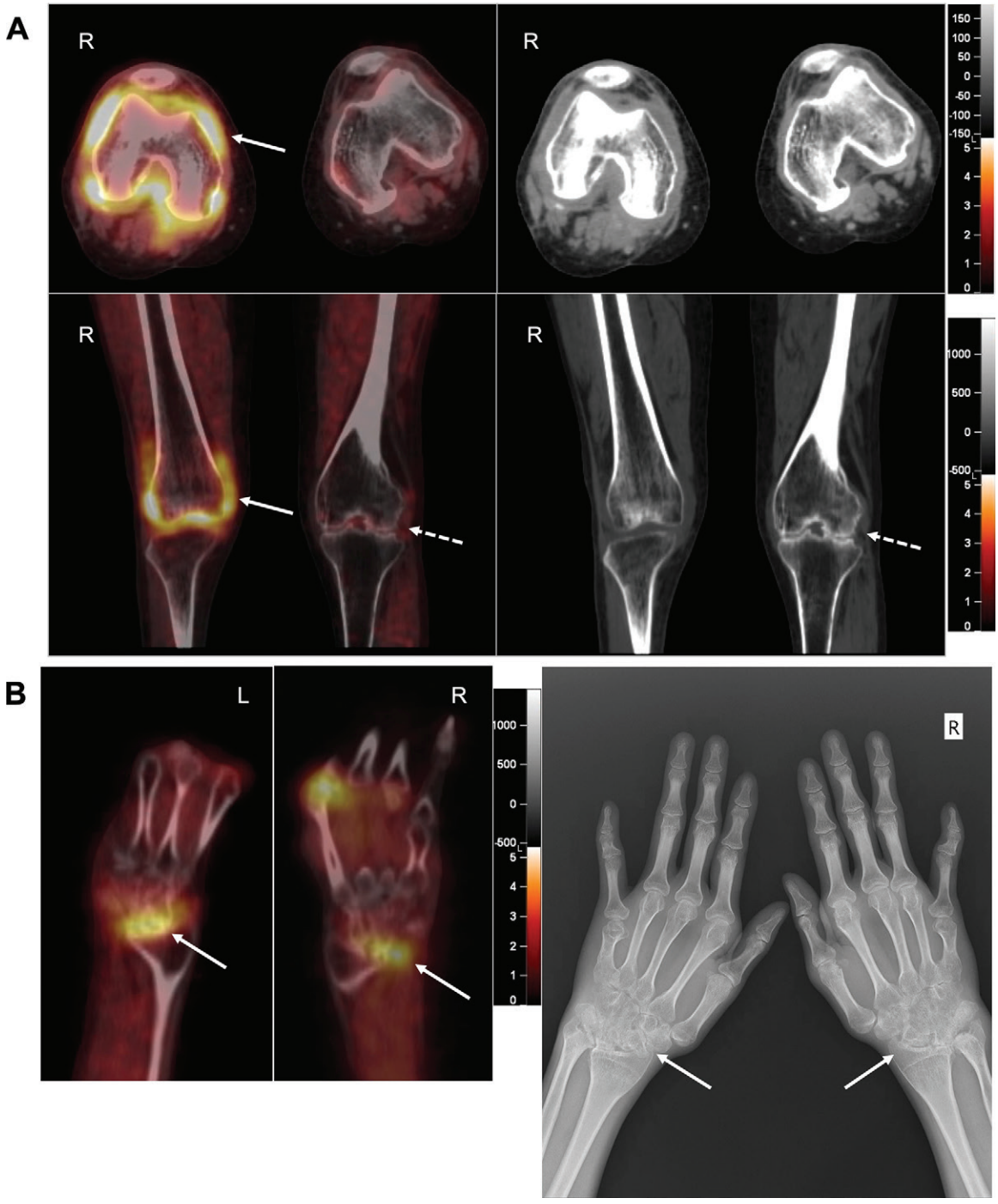

Figure 3: Fusion images show gallium 68 (^{68}Ga)-labeled fibroblast activation protein inhibitor (FAPI) uptake in the synovium of affected joints. **(A)** Axial (top row) and coronal (bottom row) ^{68}Ga-FAPI fusion (left side) and co-registered CT images (right side) in a 65-year-old woman with a 31-year history of rheumatoid arthritis. Intense ^{68}Ga-FAPI activity is in the right knee (arrows, also a tender joint at physical examination) and the synovium of the right knee is also thickened. Joint space narrowing and bone destruction is in the left knee (dashed arrows), but neither ^{68}Ga-FAPI or fluorine 18-labeled fluorodeoxyglucose uptake is observed in the joint, representing osteoarthritis without a substantial inflammatory component. The left knee is not clinically tender or swollen. **(B)** ^{68}Ga-FAPI fusion images (left images) and radiograph (right image) of the hands and wrists (^{68}Ga-FAPI PET/CT performed 6 days later than radiography) in a 25-year-old woman with a 13-year history of rheumatoid arthritis. There is increased ^{68}Ga-FAPI activity in both wrists (arrows, left), and joint space narrowing, bone destruction, and joint deformity is observed (arrows, right).

Alternatively, some of these may represent false-positive results with ^{68}Ga-FAPI or ^{18}F-FDG.

We also noted that 77 of 314 (24.5%) of the arthritic joints were not tender or swollen joints at clinical assessment but were detected at PET/CT, even though the physical examinations were performed by rheumatologists with at least 10 years of experience. It is possible that some joints that were positive for RA and detected at PET/CT might reflect a nonrheumatologic process or subclinical disease, however, we think in most cases physical examination may

Table 2: Spearman Rank Correlation Test of Assessment of Disease Activity

	PJC		PAI	
Clinical Assessment of Disease Activity	^{68}Ga-FAPI PET/CT	^{18}F-FDG PET/CT	^{68}Ga-FAPI PET/CT	^{18}F-FDG PET/CT
ESR (mm/h)				
R value	0.46	0.45	0.51	0.54
P value	.047*	.06	.04*	.02*
CRP (mg/L)				
R value	0.47	0.58	0.55	0.57
P value	.047*	.02*	.03*	.02*
Tender/swollen joint count				
R value	0.65	0.64	0.47	0.58
P value	.02*	.02*	.047*	.02*
HAQ-DI				
R value	0.72	0.52	0.54	0.51
P value	.01*	.04*	.04*	.04*
SF-36				
R value	−0.49	−0.43	−0.284	−0.28
P value	.047*	.09	.25	.27
CDAI				
R value	0.45	0.44	0.33	0.36
P value	.05	.06	.17	.13
SDAI				
R value	0.63	0.64	0.47	0.55
P value	.02*	.02*	.047*	.02*
DAS28-ESR				
R value	0.56	0.54	0.49	0.56
P value	.03*	.03*	.047*	.02*
DAS28-CRP				
R value	0.57	0.67	0.51	0.58
P value	.03*	.02*	.04*	.02*
Radiographic staging				
R value	0.54	0.57	0.53	0.49
P value	.04*	.02*	.04*	.05

Note.—CDAI = clinical disease activity index, CRP = C-reactive protein, DAS28 = disease activity score with 28-joint counts, ESR = erythrocyte sedimentation rate, FAPI = fibroblast activation protein inhibitor, FDG = fluorodeoxyglucose, HAQ-DI = health assessment questionnaire disability index, PAI = PET articular index, PJC = PET joint count, SDAI = simplified disease activity index, SF-36 = Medical Outcomes Study short form–36.

* Indicates statistical significance. *P* value corrected with false-discovery rate (Benjamini-Hochberg method) for multiple comparisons.

have missed the affected joints (≤17 arthritic joints missed in an individual participant; Fig 2, participant 6). This may result in a lower estimate of disease activity assessed by the clinical disease activity index, simplified disease activity index, or DAS28, and failed authentic disease remission by tight control treatment. Stringent criteria for disease remission are important because progressive joint destruction may occur if disease activity persists, and function may decline. Further study is necessary to investigate whether ^{68}Ga-FAPI PET/CT can help detect minimal residual disease in participants with remission or low disease activity with tight control treatment.

RA typically involves the synovial joints of the extremities, whereas the axial skeleton is usually less affected. In our study, both ^{68}Ga-FAPI and ^{18}F-FDG PET/CT helped detect atlantoaxial involvement in three of 20 (15%) participants. This may be important because atlantoaxial rheumatoid disease may cause axial migration and lead to cervical myelopathy. Other axial and central joints that can be involved in RA include temporomandibular, acromioclavicular, sternoclavicular, cricoarytenoid joints, and hip joints (14). We found that the participants with concurrent involvement in these joints had higher disease activity, higher levels of acute phase reactant, and higher PET articular index than participants with arthritis in the 28-joint area alone, suggesting axial and central joint involvement may be related to more severe rheumatoid disease.

Our study had several limitations. First, only participants with moderate or high disease activity were enrolled because we should first prove the concept of ^{68}Ga-FAPI PET/CT in detecting RA in the more severe spectrum of disease during a pilot study. Thus, the efficacy of ^{68}Ga-FAPI PET/CT in assessing disease activity in participants with clinically low disease activity or remission needs to be further elucidated. Second, FAP immunohistochemical staining in synovial tissues was

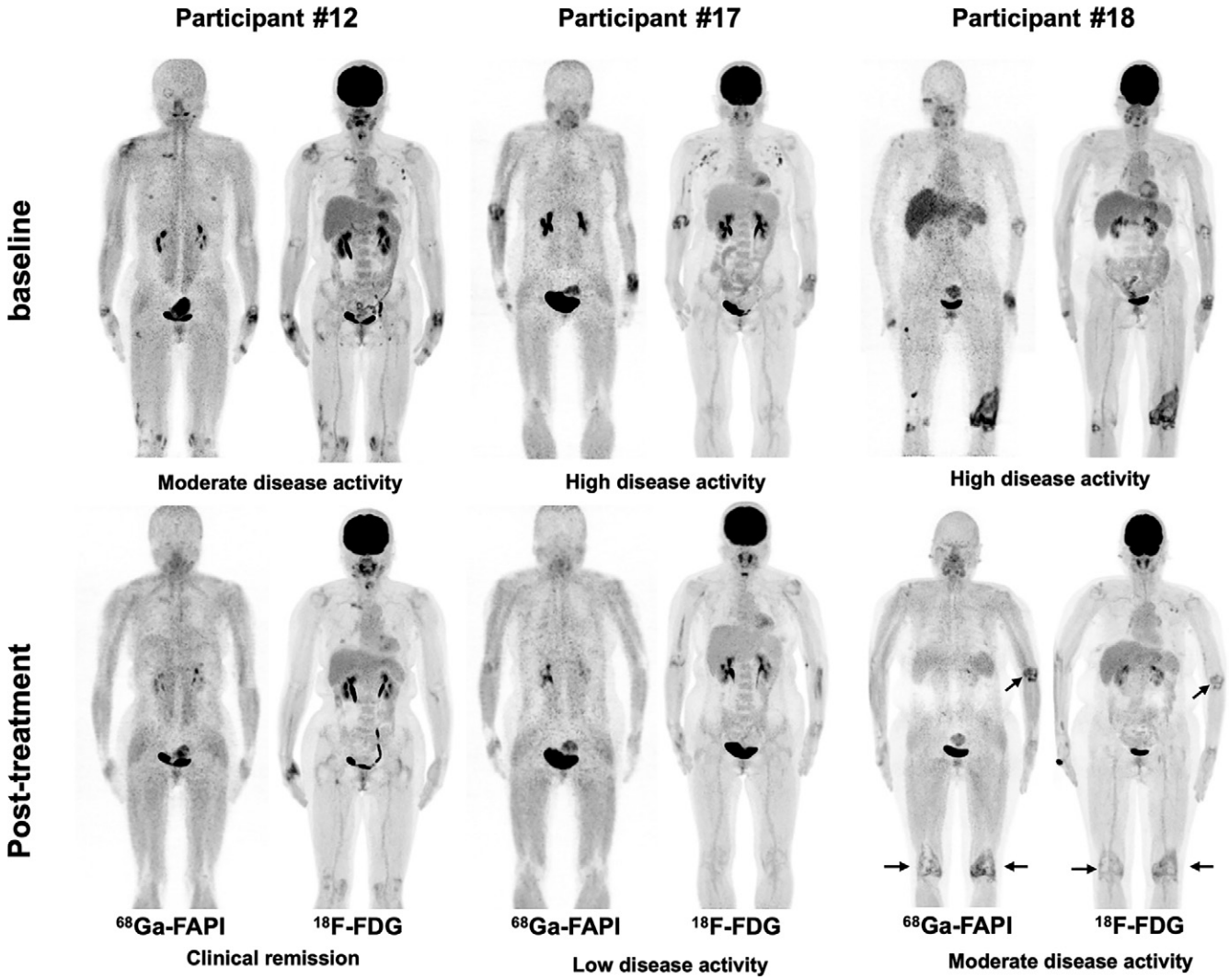

Figure 4: Pre- and posttreatment dual-tracer PET/CT in the three participants with different responses undergoing tight control treatment. Participant 12 is a 55-year-old woman with a 1-month history of rheumatoid arthritis (RA) who was treated with methotrexate, etoricoxib, tripterygium wilfordii, and iguratimod. Participant 17 is a 53-year-old woman with a 1-year history of RA who was treated with methotrexate and etanercept. Participant 18 is a 55-year-old woman with a 19-month history of RA who was treated with methotrexate, etanercept, and tripterygium wilfordii. There is residual active uptake of gallium 68 (^{68}Ga)-labeled fibroblast activation protein inhibitor (FAPI) and fluorine 18 (^{18}F)-labeled fluorodeoxyglucose (FDG) in three major joints 6 months after treatment in participant 18 (arrows).

Table 3: Clinical Assessment of Disease Activity in Participants with Follow-Up ^{68}Ga-FAPI PET/CT

	Patient 12		Patient 17		Patient 18	
Parameter	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
Clinical assessment of disease activity						
ESR (mm/h)	98	13	37	5	82	15
CRP (mg/L)	9.5	0.8	41.8	3.0	69.8	4.1
CDAI	20	2	34	4	47	21
SDAI	20.1	2.1	38.2	4.3	54	21.4
DAS28-ESR	5.5	1.9	6.2	2.1	7.6	4.4
DAS28-CRP	3.9	1.3	6.2	2.4	7.5	3.5
^{68}Ga-FAPI PET/CT						
PJC	9	0	4	1	8	3
PAI	17	0	7	1	16	7

Note.— CDAI = clinical disease activity index, CRP = C-reactive protein, DAS28 = disease activity score with 28-joint counts, ESR = erythrocyte sedimentation rate, FAPI = fibroblast activation protein inhibitor, PAI = PET articular index, PJC = PET joint count, SDAI = simplified disease activity index.

not performed in the enrolled participants but we did confirm overexpression of FAP in synovium of RA compared with participants with osteoarthritis and healthy control participants (Fig S1). Third, the PET articular index metric in our study may have lacked linearity as a scoring system, and further studies are warranted to establish a PET-based formula for better grading of the disease activity. Finally, the two readers did not read the images independently but worked together and reached a consensus for PET/CT interpretation, which may have potentially biased the result.

In summary, PET/CT with gallium 68 (^{68}Ga)-labeled fibroblast activation protein inhibitor (FAPI) demonstrated increased uptake in affected joints of participants with rheumatoid arthritis and correlated with clinical and laboratory disease markers. Furthermore, ^{68}Ga-FAPI demonstrated a greater number of joints affected and increased concentration of tracer uptake compared with fluorine 18 fluorodeoxyglucose. These results suggest that further studies are warranted to clarify the role of ^{68}Ga-FAPI in measuring disease activity in participants with rheumatoid arthritis.

Author contributions: Guarantors of integrity of entire study, **Y.L., M.L., H.Y., F.L.**; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, **Y.L., M.L., X.J., H.Y., F.L.**; clinical studies, **Y.L., Q.P., Z.Z., M.L., H.Y., F.L.**; experimental studies, **Y.L., M.L., Y.W., X.J., H.Y., F.L.**; statistical analysis, **Y.L., M.L., H.Y., F.L.**; and manuscript editing, **Y.L., Z.Z., M.L., X.J., H.Y., F.L.**

Data sharing: Data generated or analyzed during the study are available from the corresponding author by request.

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