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CONCISE REPORT

Evaluation of synovial angiogenesis in patients with rheumatoid arthritis using ^{68}Ga-PRGD2 PET/CT: a prospective proof-of-concept cohort study

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ABSTRACT

Background The study aimed to evaluate the use of positron emission tomography/computed tomography (PET/CT) with ^{68}Ga-PRGD2 as the tracer for imaging of synovial angiogenesis in patients with rheumatoid arthritis (RA).
Methods Twenty untreated active patients with RA underwent ^{68}Ga-PRGD2 PET/CT and ^{18}F-FDG PET/CT before treatment; two patients with osteoarthritis served as controls. Among the 20 patients with RA, 12 repeated the evaluations after 3-month treatment. The image findings were correlated with core variables of disease activity, including the clinical disease activity index (cDAI).
Results Our findings demonstrated that ^{68}Ga-PRGD2 specifically accumulated in the synovia with active inflammation rich in neovasculature with high-level $\alpha_v\beta_3$-integrin expression, but not in the ^{18}F-FDG-avid inflammatory lymph nodes. In patients with intense ^{18}F-FDG uptake in muscles caused by arthritic pain, we observed that ^{68}Ga-PRGD2 PET/CT was better able to evaluate disease severity than ^{18}F-FDG PET/CT. Both ^{68}Ga-PRGD2 accumulation and ^{18}F-FDG uptake changed in response to therapeutic intervention, whereas the changes of ^{68}Ga-PRGD2, not ^{18}F-FDG, significantly correlated with clinical measures of changes in the form of cDAI.
Conclusions This is the first integrin imaging study conducted in patients with RA that preliminarily indicates the effectiveness of the novel method for evaluating synovial angiogenesis.
Clinical trial registration This study has been registered online at NIH ClinicalTrial.gov (NCT01940926).

INTRODUCTION

Rheumatoid arthritis (RA), one of the most common rheumatic disorders, is characterised by the onset of synovial angiogenesis and inflammation and eventually leads to pannus formation and joint destruction.[1 2] The $\alpha_v\beta_3$-integrin is a transmembrane heterodimeric receptor that mediates cell–cell and cell–extracellular matrix adhesion.[3] The $\alpha_v\beta_3$-integrin plays a pivotal role in promoting and sustaining angiogenesis and has been identified as a biomarker of angiogenesis.[3–5] Cyclic arginine–glycine–aspartic acid (RGD) peptide is the key integrin recognition motif that can strongly bind to the $\alpha_v\beta_3$-integrin and inhibit new blood vessel formation, which make the RGD-based peptides hold a promise for imaging and treatment of diseases characterised with angiogenesis including RA.[6–9]

To date, however, no reports have presented the clinical application of integrin imaging for the evaluation of synovial angiogenesis and pannus formation, which are very important for the histopathological analysis of patients with RA. In this prospective cohort study, we evaluated the ability of RGD positron emission tomography/computed tomography (PET/CT) to assess synovial angiogenesis and monitor response to treatment in patients with RA. The results were compared with those generated by FDG PET/CT through clinical case-by-case evaluations.

PATIENTS AND METHODS

Patients

This study was approved by the Institutional Review Board of Peking Union Medical College Hospital and conducted from February 2012 to December 2013. Written informed consent was obtained from each participating patient. All of the patients with RA recruited for the study met the 1987 revised criteria of the American College of Rheumatology (ACR) for RA.[10]

We recruited 20 patients with RA (n=18 females/2 male; mean age, 49±12 years; disease duration, 36±39 months; the demographic and clinical characteristics of the patients with RA are presented in online supplementary table S1) and two patients with osteoarthritis (OA) as diseased controls. We evaluated all patients using whole-body ^{68}Ga-PRGD2 PET/CT and ^{18}F-FDG PET/CT scans. At the time of enrolment in this study, all patients were assessed for core ACR variables of disease activity, including tender joint count (TJC-28), swollen joint count (SJC-28), pain intensity score (10 cm visual analogue scale (VAS), 0.0 = no pain, 10.0 = very intensive pain), patients' global assessment of overall well-being (PtGA, 10 cm VAS) and physician's global assessment of disease severity (PyGA, 10 cm VAS); a clinical disease activity index (cDAI) was calculated as follows: cDAI=TJC-28 +SJC-28+PtGA+PyGA.[11]

Twelve patients repeated the ^{68}Ga-PRGD2 PET/CT and ^{18}F-FDG PET/CT scans and the clinical evaluations 3 months after the treatment. Two patients with RA agreed to undergo synovial biopsy before treatment.

METHODS

Details of ^{68}Ga-PRGD2 PET/CT scanning, ^{18}F-FDG PET/CT scanning, semi-quantitative

analysis, immunohistochemical analysis and statistical analysis are given in online supplementary information.

RESULTS

Comparison of ^{68}Ga-PRGD2 PET/CT with ^{18}F-FDG PET/CT

An intense accumulation of ^{68}Ga-PRGD2 occurred in the primary excretory pathways (including the kidneys and bladder) and moderate uptake occurred in the thyroid, liver, spleen and intestinal tract; the distribution of ^{68}Ga-PRGD2 in other parts of the body was low and stable and therefore able to provide an accurate evaluation of joint inflammation in the patients. The patients with RA experienced high levels of ^{68}Ga-PRGD2 accumulation in the involved joints and tendon sheaths and diffuse distribution in the lining of the synovium (figure 1B); in contrast, the OA controls experienced only slight regional tracer uptake in the affected joints (figure 1H). Moreover, the accumulation of ^{68}Ga-PRGD2 decreased with decreasing disease activity after effective treatment (figure 1D).

In contrast to the results observed in the ^{18}F-FDG PET/CT images, no accumulation of ^{68}Ga-PRGD2 was observed before treatment in the hyperplastic ^{18}F-FDG-avid lymph nodes at the bilateral axillary regions of the patients with RA (figure 1A,C). Moreover, the pain and movement disorder in patients suffering from RA may have caused intense ^{18}F-FDG uptake in the related muscles, which could have significantly influenced the evaluation of disease severity in the joints with ^{18}F-FDG PET/CT. However, the distribution of ^{68}Ga-PRGD2 was much less varied in the skeletal muscles, bone marrow and myocardium than that of ^{18}F-FDG; thus, ^{68}Ga-PRGD2 introduced less background noise and prevented possible evaluation bias in the assessment of disease severity and treatment response (figure 1E, F).

Correlation of PET/CT images with clinical parameters

The maximum standardised uptake value (SUV_{max}) of ^{68}Ga-PRGD2 was significantly correlated with the SUV_{max} of ^{18}F-FDG in the large joints before and after treatment (r=0.60 and 0.36, respectively; both p<0.001). Additionally, the SUV_{max} of ^{68}Ga-PRGD2 was significantly correlated with TJC and SJC before and after treatment (p<0.001) (table 1).

Three months after treatment, the patients with RA who repeated PET/CT were assigned to a responder group (n=9) or a poor-responder group (n=3) according to the cDAI good
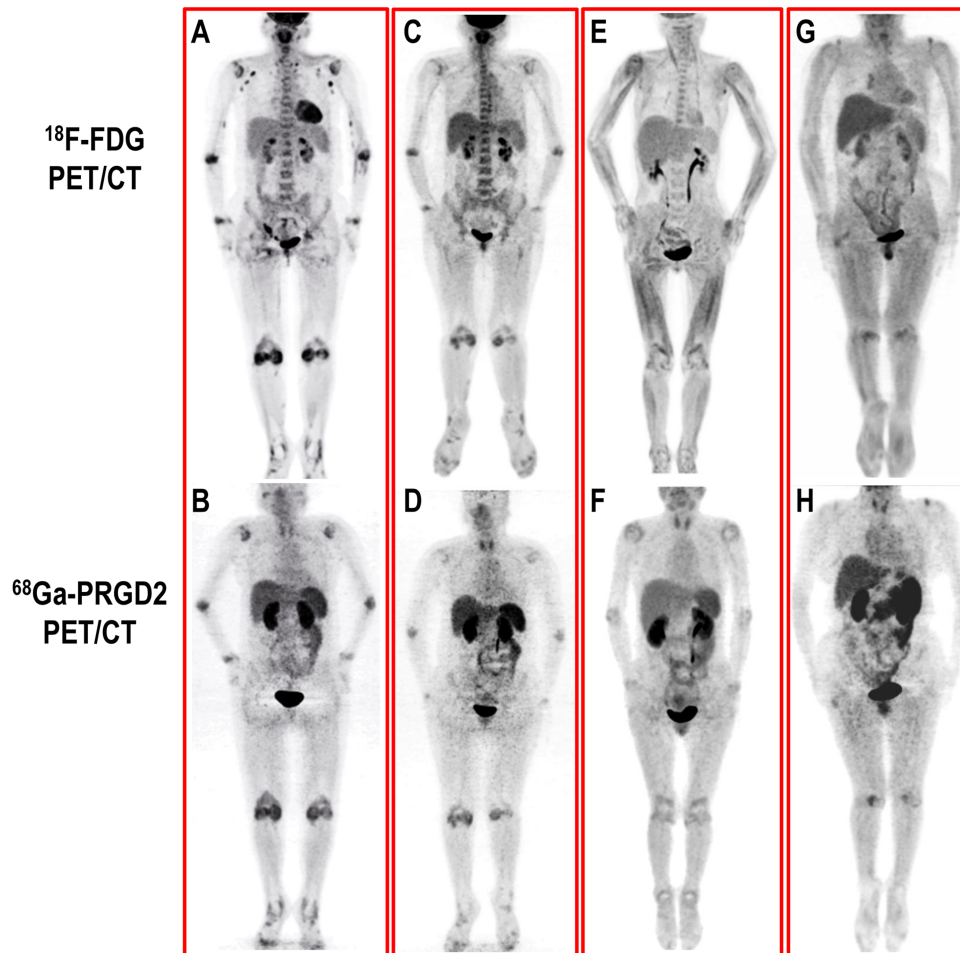

Figure 1 Comparison of the distribution of ^{18}F-FDG and ^{68}Ga-PRGD2 in patients with rheumatoid arthritis (RA) and osteoarthritis (OA). (A, B) In a patient with RA (F, 48 years) with a clinical disease activity index (cDAI) of 28.0, intense ^{18}F-FDG uptake was observed in the inflammatory synovia and axillary lymph nodes, whereas ^{68}Ga-PRGD2 accumulated specifically in the synovia. (C, D) After successful treatment (cDAI=6.0), ^{18}F-FDG uptake and ^{68}Ga-PRGD2 accumulation significantly decreased in the joints. (E, F) In another patient with RA, the joint pain caused intense ^{18}F-FDG uptake in the muscles; this accumulation significantly influenced the evaluation of disease using ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) but had no effect on the distribution of ^{68}Ga-PRGD2. (G, H) The regional uptake of ^{18}F-FDG and the accumulation of ^{68}Ga-PRGD2 in the shoulders and knees of an OA patient (M, 60 years) were significantly different from the diffuse synovial involvement in the patients with RA.

Table 1 Correlation between the uptake of ^{18}F-FDG and the accumulation of ^{68}Ga-PRGD2 and the tender joint count and swollen joint count in patients with rheumatoid arthritis

		Pretreatment (n=20)		Post-treatment (n=12)	
		TJC	SJC	TJC	SJC
SUV$_{max}$ of ^{68}Ga-PRGD2	r	0.44	0.22	0.43	0.33
	p	<0.001	<0.001	<0.001	<0.001
SUV$_{max}$ of ^{18}F-FDG	r	0.37	0.12	0.44	0.39
	p	<0.001	<0.001	<0.001	<0.001

SJC, swollen joint count; SUV$_{max}$, maximal standardised uptake value; TJC, tender joint count.

response criteria (defined as achieving ≥50% improvement of cDAI or cDAI ≤2.8 after treatment). The SUV$_{max}$ of ^{18}F-FDG and ^{68}Ga-PRGD2 decreased significantly after treatment in the responder group (p<0.001). In contrast, the SUV$_{max}$ of ^{18}F-FDG and ^{68}Ga-PRGD2 increased significantly in the poor-responder group (p=0.001 and p=0.002, respectively) (see online supplementary table S2).

We analysed the correlation between the change in SUV$_{max}$ (ΔSUV$_{max}$) and the change in clinical parameters after treatment. We observed that the reduction in ^{68}Ga-PRGD2 uptake in the affected joints was significantly correlated with the ΔPtGA, ΔPyGA and ΔcDAI (p<0.05), whereas the reduction in ^{18}F-FDG uptake after treatment was significantly correlated with ΔPtGA and ΔPyGA (p<0.05) but not with ΔcDAI (p=0.083) (table 2).

Histopathological features of the RA synovium

We examined the histopathology and expression of $\alpha_v\beta_3$-integrin in the synovia of two patients with RA to corroborate relevant findings with the ^{68}Ga-PRGD2 PET/CT findings. In agreement with the intense ^{68}Ga-PRGD2 accumulation in the affected joint synovium (see online supplementary figure S1A,B), high levels of $\alpha_v\beta_3$-integrin were selectively expressed on the endothelial cells of the synovial blood vessels (see online supplementary figure S1C). An extensive vascular network with ongoing angiogenesis and proliferation was observed in the synovium, as demonstrated by the positive staining of VEGF, CD34 and Ki67 (see online supplementary figure S1D–S1F).

DISCUSSION

Synovial angiogenesis and pannus formation are major histopathological findings in patients with RA.[1][2] The development of a new and reliable approach is needed to assess synovial neovasculature and its response to treatment.[12] In the last decade, numerous studies have demonstrated that ^{18}F-FDG PET/CT is a sensitive technique for evaluating disease activity and treatment response in patients with RA.[13–15] However, the mechanism behind ^{18}F-FDG uptake is only associated with elevated glucose metabolism.[16]

^{68}Ga-PRGD2 is specifically designed to target the endothelial cells of neovasculature that express $\alpha_v\beta_3$-integrin at high levels.[17][18] Therefore, ^{68}Ga-PRGD2 PET/CT represents a specific method for evaluating angiogenesis. As demonstrated by the present study, ^{68}Ga-PRGD2 was found to be typically distributed in a diffuse manner along the lining of the synovium of the affected joints and tendon sheaths of patients with RA, whereas the accumulation of ^{68}Ga-PRGD2 was confined to a specific diseased area in patients with OA. Interestingly, we also found that ^{68}Ga-PRGD2 did not accumulate in the ^{18}F-FDG-avid axillary lymph nodes commonly observed in patients with RA.[19] In patients with intense ^{18}F-FDG uptake in muscles caused by arthritic pain, we observed that ^{68}Ga-PRGD2 PET/CT was better able to evaluate disease severity than

^{18}F-FDG PET/CT. Additionally, in response to therapeutic intervention, the changes of ^{68}Ga-PRGD2, not ^{18}F-FDG, significantly correlated with clinical measures of changes in the form of cDAI.

To the best of our knowledge, this is the first study conducted in humans to investigate the use of integrin imaging (specifically ^{68}Ga-PRGD2 PET/CT) for the non-invasive measurement of synovial angiogenesis in patients with active RA. We compared the findings of this technique with the ^{18}F-FDG PET/CT findings of the same patients. We provided histopathological confirmation showing high-level expression of $\alpha_v\beta_3$-integrin on the neovasculature endothelial cells of the ^{68}Ga-PRGD2-avid RA synovium that were consistent with previous immunohistochemical findings in synovial tissue.[9][20]

Some limitations apply to the present study. First, the number of enrolled patients with RA was small. However, each patient underwent ^{68}Ga-PRGD2 PET/CT and ^{18}F-FDG PET/CT scanning, and 12 patients repeated the scans after 3-month treatment; thus, the preliminary results of this study support a proof-of-concept study. Second, the study lacks a sufficient number of control patients with OA or other forms of arthritis. An additional study is required to recruit a wide variety of patients with arthritis to determine the sensitivity, specificity and accuracy of ^{68}Ga-PRGD2 PET/CT in diagnosing RA. Studies with more cases are needed to correlate the image findings related to post-treatment changes with the clinical response and final prognosis of patients with RA.

In conclusion, this prospective cohort study demonstrates that ^{68}Ga-PRGD2 PET/CT is a specific method for identifying and assessing inflammatory synovial angiogenesis in patients with RA. In contrast to ^{18}F-FDG, ^{68}Ga-PRGD2 did not accumulate in areas such as the axillary lymph nodes with reactive hyperplasia and the strenuous skeletal muscles. Therefore, ^{68}Ga-PRGD2

Table 2 Correlation between the changes in SUV$_{max}$ in ^{68}Ga-PRGD2 PET/CT and ^{18}F-FDG PET/CT and the changes in clinical parameters of patients with RA (n=12) before and after 3-month treatment

	ΔSUV$_{max}$ of ^{68}Ga-PRGD2		ΔSUV$_{max}$ of ^{18}F-FDG	
	r	p Value	r	p Value
ΔVAS	0.39	0.215	0.65	0.021
ΔPtGA	0.62	0.033	0.61	0.034
ΔPyGA	0.60	0.040	0.72	0.009
ΔcDAI	0.60	0.039	0.52	0.083

Δ, changes between the baseline and the post-treatment evaluation; cDAI, clinical disease activity index; r, correlation coefficient; PET, positron emission tomography; PtGA, patient's global assessment of overall well-being; PyGA, physician's global assessment; RA, rheumatoid arthritis; SUV$_{max}$, maximal standardised uptake value of a tracer; VAS, visual analogue scale of joint pain.

PET/CT is a useful tool for assessing synovial angiogenesis and monitoring treatment responses in patients with RA.

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Competing interests None.

Patient consent Obtained.

Ethics approval This study has been approved by the Institutional Review Board of Peking Union Medical College Hospital (S-532).

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REFERENCES

1. Koch AE. Angiogenesis as a target in rheumatoid arthritis. *Ann Rheum Dis* 2003;62 (suppl 2):ii60–7.
2. Conaghan PG, O'Connor P, McGonagle D, *et al*. Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. *Arthritis Rheum* 2003;48:64–71.
3. Hynes RO. Integrins: versatility, modulation, and signaling in cell adhesion. *Cell* 1992;69:11–25.
4. Brooks PC, Clark RA, Cheresh DA. Requirement of vascular integrin alpha v beta 3 for angiogenesis. *Science* 1994;264:569–71.
5. Niu G, Chen X. Why integrin as a primary target for imaging and therapy. *Theranostics* 2011;1:30–47.
6. Zhu Z, Miao W, Li Q, *et al*. [99m]Tc-3PRGD2 for integrin receptor imaging of lung cancer: a multicenter study. *J Nucl Med* 2012;53:716–22.
7. Chen X, Liu S, Hou Y, *et al*. MicroPET imaging of breast cancer alphav-integrin expression with ^{64}Cu-labeled dimeric RGD peptides. *Mol Imaging Biol* 2004;6:350–9.
8. Wilder RL. Integrin alpha V beta 3 as a target for treatment of rheumatoid arthritis and related rheumatic diseases. *Ann Rheum Dis* 2002; 61(suppl 2):ii96–9.
9. Storgard CM, Stupack DG, Jonczyk A, *et al*. Decreased angiogenesis and arthritic disease in rabbits treated with an alphavbeta3 antagonist. *J Clin Invest* 1999;103:47–54.
10. Arnett FC, Edworthy SM, Bloch DA, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
11. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol* 2005;23:S100–8.
12. Naredo E, Collado P, Cruz A, *et al*. Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: predictive value in disease activity and radiologic progression. *Arthritis Rheum* 2007;57:116–24.
13. Goerres GW, Forster A, Uebelhart D, *et al*. F-18 FDG whole-body PET for the assessment of disease activity in patients with rheumatoid arthritis. *Clin Nucl Med* 2006;31:386–90.
14. Elzinga EH, van der Laken CJ, Comans EF, *et al*. ^{18}F-FDG PET as a tool to predict the clinical outcome of infliximab treatment of rheumatoid arthritis: an explorative study. *J Nucl Med* 2011;52:77–80.
15. Okamura K, Yonemoto Y, Arisaka Y, *et al*. The assessment of biologic treatment in patients with rheumatoid arthritis using FDG-PET/CT. *Rheumatology (Oxford)* 2012;51:1484–91.
16. Izuishi K, Yamamoto Y, Sano T, *et al*. Molecular mechanism underlying the detection of colorectal cancer by ^{18}F-2-fluoro-2-deoxy-D-glucose positron emission tomography. *J Gastrointest Surg* 2012;16:394–400.
17. Lang L, Li W, Guo N, *et al*. Comparison study of [18F]FAl-NOTA-PRGD2, [18F] FPPRGD2, and [68Ga]Ga-NOTA-PRGD2 for PET imaging of U87MG tumors in mice. *Bioconjug Chem* 2011;22:2415–22.
18. Guo N, Lang L, Li W, *et al*. Quantitative analysis and comparison study of [18F] AlF-NOTA-PRGD2, [18F]FPPRGD2 and [68Ga]Ga-NOTA-PRGD2 using a reference tissue model. *PLoS ONE* 2012;7:e37506.
19. Seldin DW, Habib I, Soudry G. Axillary lymph node visualization on F-18 FDG PET body scans in patients with rheumatoid arthritis. *Clin Nuclear Med* 2007;32:524–26.
20. Johnson BA, Haines GK, Harlow LA, *et al*. Adhesion molecule expression in human synovial tissue. *Arthritis Rheum* 1993;36:137–46.

Online supplementary text of the methods

^{68}Ga-PRGD2 PET/CT scanning

The cyclic RGD peptide is modified by PEGylated dimerization to form PRGD2 and chelated with 1,4,7-triazacyclononane-1,4,7-triyltriacetic acid (NOTA).[8-10] ^{68}Ga-PRGD2 is synthesized on site (immediately before injection) with a radiochemical purity exceeding 97%. A Biograph 64 TruePoint TrueV PET/CT system (Siemens Medical Solutions, Erlangen, Germany) was used for scanning. For each patient, 1.85 MBq (0.05 mCi) of ^{68}Ga-PRGD2 per kilogram of body weight was injected intravenously.

^{18}F-FDG PET/CT scanning

Patients underwent ^{18}F-FDG PET/CT from the skull base to the planta within five days of the ^{68}Ga-PRGD2 PET/CT scan. ^{18}F-FDG was produced on site using Cyclotron RDS-111 (CTI, Knoxville, TN, USA). The same PET/CT system was used for scanning. Before the examinations, each patient was asked to fast for at least 4 h. The blood glucose level of the patient was within normal limits (lower than 6.4 mmol/L) before the ^{18}F-FDG was injected at a dosage of 5.55 MBq (0.15 mCi) per kilogram of body weight.

Semi-quantitative analysis

Two blinded independent nuclear medicine experts conducted the assessment of PET/CT images and reached a consensus when there was disagreement. The same nuclear medicine physicians examined all of the images using the same standard for the final analysis. A Siemens MMWP workstation was used for post-processing. For each patient, the volume of interest (VOI) was drawn over 10 large joints (bilateral shoulders, elbows, wrists, knees, and ankle) and the maximum standardized uptake values (SUV_{max}) were recorded.

Immunohistochemical analysis

To confirm synovial angiogenesis and $\alpha_V\beta_3$-integrin expression, we conducted an

immunohistochemical analysis of the synovia of two patients with active RA to corroborate their PET/CT findings. Cryosections (4-μm thick) were obtained and subsequently incubated at room temperature with one of the following monoclonal antibodies: integrin $\alpha_V\beta_3$ (clone BV3, Abcam, USA); CD34 (clone QBEnd/10, Leica Biosystems, Germany); Ki-67 (clone EP5, Epitomics, USA) and vascular endothelial growth factor (VEGF; clone EP1176Y, Biocare, USA). The samples were incubated with homologous secondary antibodies conjugated with horseradish peroxidase (HRP) and then diaminobenzidine (DAB) (K4065, DAKO, USA).

Statistical analysis

The Kolmogorov-Smirnov test was conducted to evaluate the normality of continuous data. A Pearson's correlation coefficient was calculated to assess the correlation between the SUV_{max} of ^{68}Ga-PRGD2 and ^{18}F-FDG in the joints. The paired-sample t test was used to compare SUV_{max} before and after treatment. Finally, the correlations between changes in SUV_{max} and changes in clinical parameters were calculated using Spearman's rho test. All of the statistical analyses were performed using SPSS (version 21.0, SPSS Inc., Chicago, IL, USA), and $p<0.05$ was considered to be statistically significant.

Table S1. Demographic characteristics of the enrolled patients with RA

No.	Gender	Age (years)	Disease duration (months)	Medication	PET/CT follow-up
1	Female	48	116	MTX, LEF, PRED	Yes
2	Female	26	46	MTX, LEF, PRED	Yes
3	Male	57	5	MTX, NSAIDS	Yes
4	Female	49	28	MTX, NSAIDS	Yes
5	Female	35	11	MTX, HCQ, PRED	Yes
6	Female	39	12	MTX	Yes
7	Female	54	27	MTX	Yes
8	Female	57	10	MTX, NSAIDS	Yes
9	Female	50	126	MTX	Yes
10	Female	53	16	MTX, NSAIDS	Yes
11	Female	27	29	MTX, PRED	Yes
12	Female	38	8	ETN	Yes
13	Female	54	27	MTX, NSAIDS	No
14	Female	43	23	MTX, NSAIDS	No
15	Female	65	60	MTX, NSAID	No
16	Female	57	6	MTX, LEF, PRED	No
17	Male	58	34	MTX, PRED	No
18	Female	42	120	MTX	No
19	Female	66	1	MTX, PRED	No
20	Female	70	24	MTX	No

RA, rheumatic arthritis; MTX, methotrexate; LEF, leflunomide; PRED, prednisone; NSAIDS, nonsteroidal anti-inflammatory drugs; HCQ, hydroxychloroquine; ETN, etanercept.

Table S2. Comparison of the accumulation of ^{68}Ga-PRGD2 and the uptake of ^{18}F-FDG in the responders and poor-responders among the patients with RA

	Pre-treatment	Post-treatment	p
Responders (number of joints assessed: 90)			
SUV$_{max}$ of ^{68}Ga-PRGD2	2.23 ±1.31	1.32 ± 0.83	<0.001
SUV$_{max}$ of ^{18}F-FDG	2.48 ± 1.48	1.69 ± 0.64	<0.001
Poor-responders (number of joints assessed: 30)			
SUV$_{max}$ of ^{68}Ga-PRGD2	1.42 ± 0.83	1.97 ± 0.97	0.002
SUV$_{max}$ of ^{18}F-FDG	1.92 ± 1.10	2.89 ± 1.18	0.001

Data are depicted as the mean ± standard deviation. The RA patients who achieved 50% or greater improvement in cDAI or cDAI≤2.8 after treatment were defined as responders; the others were classified as poor-responders.
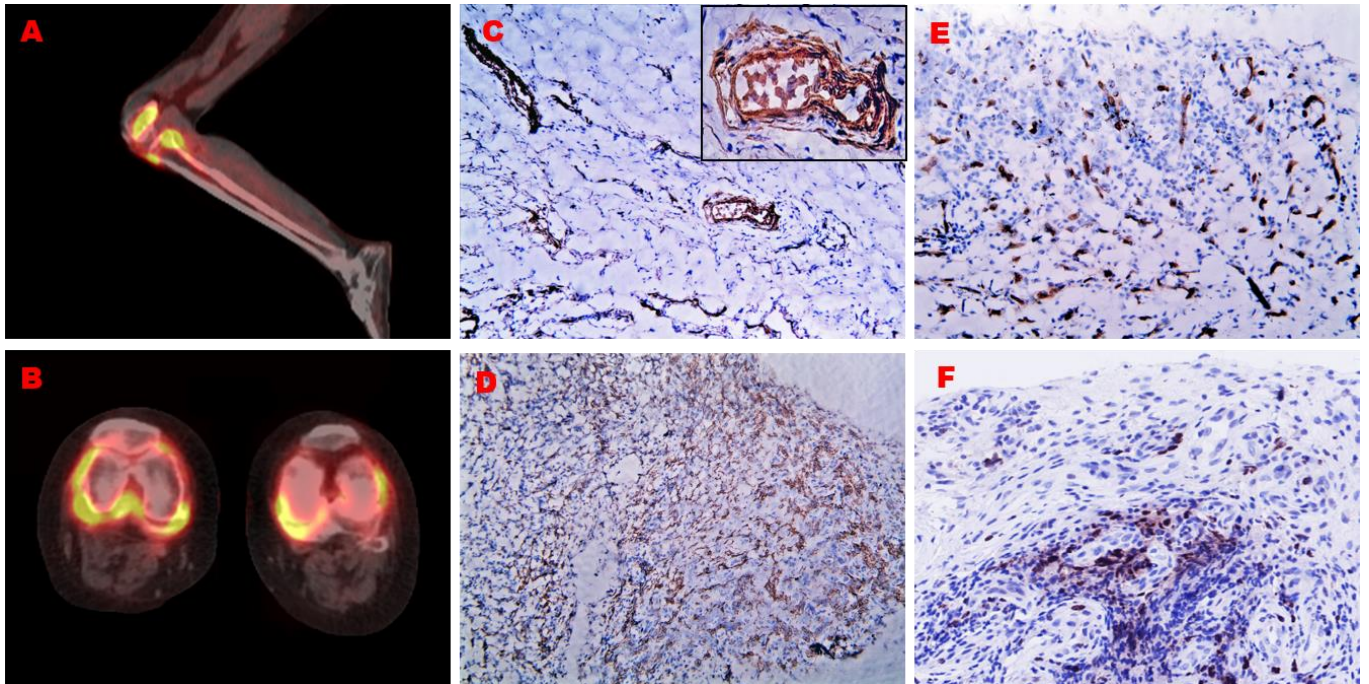
Figure S1. ^{68}Ga-PRGD2 PET/CT images and immunohistochemical stains of the knee synovium of a patient (F, 54 y) with active rheumatoid arthritis. **A and B:** The sagittal and transaxial views using PET/CT demonstrate broad intense ^{68}Ga-PRGD2 accumulation in the synovium of the inflammatory knee joint. **C:** High levels of expression of the $\alpha_V\beta_3$-integrin were observed in the vascular endothelial cells (the inset figure demonstrates the magnified view of a blood vessel). **D and E:** The vascular endothelial growth factor (VEGF) and CD34 stains indicate an extensive vascular network in the inflammatory synovium. **F:** Positive nuclear expression of Ki-67 indicates active proliferation. (Magnification 200×)