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.

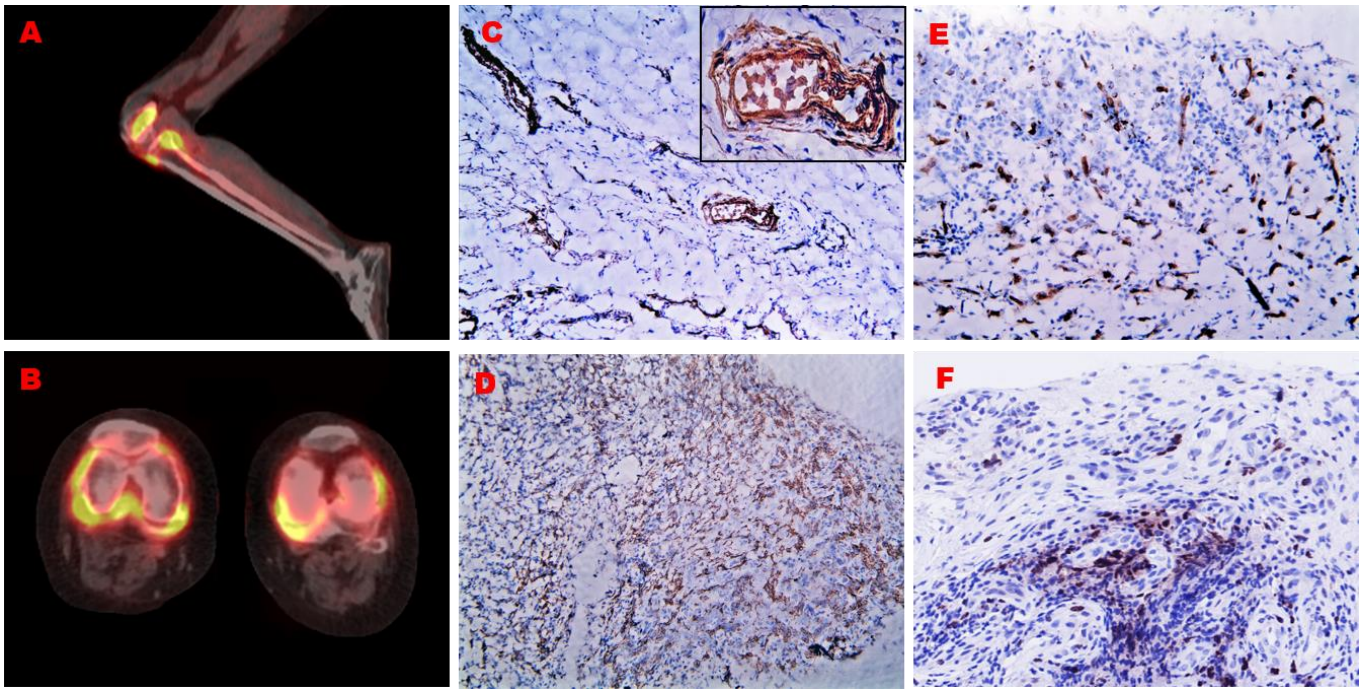

Figure S1. ^{68}Ga-PRGD2 PET/CT images and immunohistochemical stains of the knee synovium of a patient (F, 54 y) with active rheumatoid arthritis. **A and B:** The sagittal and transaxial views using PET/CT demonstrate broad intense ^{68}Ga-PRGD2 accumulation in the synovium of the inflammatory knee 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×)