Detection of Subclinical Synovitis with Macrophage Targeting and Positron Emission Tomography in Patients with Rheumatoid Arthritis without Clinical Arthritis

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ABSTRACT. ***Objective.*** To determine whether macrophage targeting by (R)-^{11}C-PK11195 positron emission tomography (PET) can visualize subclinical joint inflammation in patients with rheumatoid arthritis (RA) without clinical arthritis during or after treatment, with flare as clinical outcome measure.

Methods. (R)-^{11}C-PK11195 PET and contrast-enhanced magnetic resonance imaging (MRI) of hands/wrists were performed in 29 patients with RA without clinical arthritis. (R)-^{11}C-PK11195 PET uptake (semiquantitative score 0–3) in metacarpophalangeal, proximal interphalangeal, and wrist joints (i.e., 22 joints per patient) was scored and summed to obtain a cumulative PET score (range 0–66). Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) was performed on similar joints. Synovitis and bone marrow edema scores (> 1) were summed to obtain a cumulative MRI score (range 0–288). Occurrence of flare was determined during 3-year followup.

Results. Flare was observed in 17/29 patients (59%). (R)-^{11}C-PK11195 PET showed enhanced tracer uptake in 16/29 patients (55%), of which 11 (69%) developed a flare. Highest cumulative PET scores (> 6, n = 3) corresponded with highest cumulative MRI scores (> 39) and were related to development of flare in hands/wrists within 6 months. Cumulative PET scores of patients developing a flare were higher than those of patients without a flare [median (interquartile range) 2 (0–4.5) vs 0 (0–1), $p < 0.05$]. In contrast, no significant differences were found between cumulative MRI scores of patients with and without a flare.

Conclusion. (R)-^{11}C-PK11195 PET showed enhanced uptake, pointing to presence of subclinical synovitis in over half of patients without clinical arthritis. (R)-^{11}C-PK11195 PET may be of value for prediction of exacerbation of RA, since cumulative PET scores > 1 were associated with development of flare within 3 years. (First Release Oct 1 2014; J Rheumatol 2014;41:2145–52; doi:10.3899/ jrheum.140059)

Key Indexing Terms:
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Remission of disease is the best possible outcome of treatment regimens in rheumatoid arthritis (RA), and has become a realistic goal because of intensified disease-modifying antirheumatic drug (DMARD) therapies and biologics[1]. However, definitions of clinical remission, including the most recent 2011 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) definition[2,3], are all based on clinical signs, laboratory values, and patient- (and physician-) reported measures, and may not rule out the presence of subclinical synovitis.

Detection of subclinical disease activity may be meaningful because progressive joint damage occurs in 15% of patients with RA who have achieved persistent clinical remission[4,5]. Subclinical synovitis can only be detected by advanced and sensitive imaging techniques such as ultrasound (US), magnetic resonance imaging (MRI), and positron emission tomography (PET)[6,7]. MRI is a highly sensitive tool for identifying synovitis and bone marrow

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edema, both variables of joint inflammation. It was demonstrated that the majority of patients with RA in clinical remission still showed signs of synovitis and/or bone marrow edema on MRI, which was proposed as an explanation for the proceeding structural deterioration in these patients[8,9,10,11,12]. Further, US abnormalities are frequently present in RA remission, and an association between (Power Doppler) US signs of synovitis and occurrence of flare and radiographic disease progression in RA remission has been found by several research groups, underlining the significance of imaging of subclinical synovitis[13]. Despite these promising results, there is a substantial group of patients that exhibits MRI and/or US signs of synovitis without clinical consequences, leaving room for other imaging techniques that could contribute to specificity[9,14].

PET is a relatively new but promising technique for the imaging of arthritis. Rather than the imaging of anatomic and/or local perfusion differences as performed with MRI and US, PET visualizes pathophysiological changes at a molecular level. The technique may therefore provide additional information in the depiction of subclinical synovitis. PET with ^{18}F-fluorodeoxyglucose (^{18}F-FDG), a radioligand that accumulates in metabolically active cells, can visualize arthritis in patients with RA[15] and may be useful in monitoring the response to therapy in RA[16]. ^{18}F-FDG accumulation is, however, not restricted to inflammatory cells, but occurs in all cells with an increased metabolic rate. For more specific targeting of inflammation, macrophage-specific tracers, such as (R)-^{11}C-PK11195 [1-(2-chlorophenyl)-N-methyl-N-(1-methylpropyl)-3-isoquinoline carboxamide], were developed[17]. PK11195 binds to the translocator protein (TSPO), which is found on the outer mitochondrial membrane, where it has a major function in the transport of cholesterol into the mitochondrion[18]. (R)-^{11}C-PK11195 can be used as a radioligand for inflammatory diseases because TSPO is upregulated in activated macrophages and microglia[19,20]. Previous studies have shown that (R)-^{11}C-PK11195 PET is able to detect subclinical disease activity in patients with preclinical and established RA[7,21].

Our prospective study aimed to explore whether (R)-^{11}C-PK11195 PET can visualize subclinical inflammation in hand and/or wrist joints of treated patients with RA without clinical arthritis. In addition, the relationship between baseline PET outcome and occurrence of clinical disease flare was examined, including comparison to MRI performance.

MATERIALS AND METHODS

Patients and study protocol. Rheumatologists of the VU University Medical Center and Jan van Breemen research institute/Reade referred patients with RA who were in clinical remission. Subsequently, patients (n = 29) fulfilling the following criteria were included: previous diagnosis with RA according to the ACR criteria (1987), age ≥ 18 years, and absence of any tender or swollen joints according to a 44-tender and 44-swollen joint count[22]. Exclusion criteria were pregnancy or breast-feeding, pacemaker, use of a benzodiazepine receptor agonist 10 days prior to PET scanning, or previous exposure to radioactivity with a yearly cumulative dose of ≥ 5 mSv. Use of DMARD and biologicals was allowed. Following inclusion, high (spatial) resolution (R)-^{11}C-PK11195 PET and contrast-enhanced MRI of hands and wrists were performed. Following PET and MRI, patients were evaluated for clinical disease activity in routine clinical practice visits by their treating rheumatologists, every 3–6 months. On top of these clinical reports, at 3 years of followup, a 44-joint tender joint count and 44-joint swollen joint count were performed for each patient by a blinded clinical investigator. From these evaluations, the presence or absence of flare could be determined. Flare was defined as (1) occurrence of clinical arthritis in > 1 joint, or (2) occurrence of clinical arthritis in 1 joint plus 1 of the following criteria: (a) clinical arthritis (i.e., minimal 1 swollen joint) was reported during at least 1 additional visit later during followup, (b) flare of clinical arthritis resulted in treatment regimen modification aimed at reduction of clinical disease activity, or (c) Disease Activity Score at 28 joints (DAS28) > 3.2 or DAS44 > 2.4. Ethical approval was obtained from the ethics committee of the VU University Medical Center and informed consent was given by all patients prior to inclusion.

PET protocol and data analysis. At baseline, left and right metacarpophalangeal (MCP) 1–5, proximal interphalangeal (PIP) 1–5, and both wrist joints (i.e., 22 joints per patient) were evaluated with (R)-^{11}C-PK11195 PET. PET scanning was performed using a double-layer emission computed axial tomography high resolution research tomograph (CTI/Siemens), which is a small animal and human brain 3-D scanner with high spatial resolution (about 3 mm full width at half maximum) and high sensitivity[23]. Patients were lying in prone position with their arms extended above their heads. Both hands and wrists were placed in the scanner and fixed to prevent movement artefacts. Ten minutes after intravenous injection of (R)-^{11}C-PK11195 (mean dose 415 ± 27 MBq), a static emission scan was performed during 20 min, which was followed by a transmission scan of 7 min[24]. Measured PET data were normalized and a correction was performed for scatter, randoms, attenuation, decay, and dead time. Data reconstruction was executed using an iterative 3-D ordinary Poisson ordered-subsets expectation maximization algorithm[25] with 8 iterations and 16 subsets. Joint and background uptake of (R)-^{11}C-PK11195 were semiquantitatively scored (on a 4–point scale: 0 = absent, 1 = faint, 2 = moderate, 3 = intense), as described previously[7]. Background (R)-^{11}C-PK11195 uptake was present in intrinsic hand muscle, region of the bone marrow, and in soft tissue around the nails as was found and described previously[7]. Final scores per joint were calculated by subtraction of background scores from joint scores. Joints were considered as positive if the final score was ≥ 1. At a patient level, PET scans were considered as positive if at least 1 joint with a score ≥ 1 was present. For a cumulative PET score per patient, final individual joint scores of both hands and wrists were summed, resulting in a maximal achievable cumulative score of 66. Scans were presented in random order to 2 independent observers who were blinded to clinical data and MRI results. For analysis, consensus scores of the 2 observers were used.

MRI protocol and data analysis. MRI examinations of the left hand, right hand, and wrist joints were performed with a 1.5-T whole body MR scanner (Siemens Sonata). Patients were in prone position with their arms extended above their heads. Hands were folded around a foam cushion and a large receiving flex-coil was placed around the dorsum of the hands. Sequences were chosen according to Outcome Measures in Rheumatology Clinical Trials (OMERACT) guidelines. Short T1 inversion recovery images were obtained in coronal orientation (for each hand, 13 slices of 3 mm with 0.6 mm gap, repetition time TR 6550 ms, echo time TE 27 ms, inversion time TI 150 ms, 2 averages). Before and after contrast injection with gadopentetate dimeglumine (Magnevist), a 3-D T1-weighted magnetization prepared rapid acquisition gradient echo (TR/TE/TI = 1780/2/1000 ms) was performed with isotropic 0.7 mm resolution. These 3-D images were reconstructed as coronal and transverse 1 mm slices.

Synovitis and bone marrow edema of the hands and wrists were scored according to the OMERACT RA MRI Scoring (RAMRIS) system[26], with

synovitis and bone marrow edema scored on a 0–3 semiquantitative scale (synovitis: 0 = normal, 1 = mild, 2 = moderate, 3 = severe; bone marrow edema: 0 = no edema, 1 = 1–33% of bone edematous, 2 = 34–66% of bone edematous, 3 = 67–100% of bone edematous).

For MRI, identical joints (all MCP, PIP, and both wrist joints), as for PET, were imaged and scored for synovitis and (proximal/distal) bone marrow edema. Therefore, our scoring method included the RAMRIS score of the dominant hand (range 0–90), which has been validated and applied in several studies[27], but was expanded by additional scoring of synovitis and (proximal/distal) bone marrow edema of MCP 1 and PIP 1–5 joints of the dominant hand, as well as PIP 1–5, MCP 1–5, and wrist joints of the nondominant hand.

For our analysis, joints were considered positive if a score ≥ 2 synovitis or bone edema was found. At a patient level, MRI scans were positive if at least 1 joint with a score ≥ 2 synovitis or bone marrow edema was present. Score 1 was excluded because mild synovitis or bone edema can be present on MRI scans of control subjects as well, and the interpretation of this score is still uncertain[28,29].

A cumulative MRI score (excluding score 1, range 0–288) was composed by summing up all individual synovitis plus bone marrow edema joint scores of both hands and wrists. In addition, original RAMRIS scores (that include scores 1 for synovitis and bone marrow edema) of the dominant hand were determined and a cumulative RAMRIS score (range 0–90) was computed.

All scans were read by 2 observers who were blinded to clinical data and PET results. MRI scans were scored in a joint session and consensus scores were used for analysis.

Statistical analysis. Differences in cumulative scores between groups with and without a flare were evaluated with non-parametric Mann-Whitney U tests. A p value < 0.05 was regarded as statistically significant. Results were expressed as means and SD, or median and interquartile range (IQR) where appropriate. All statistical tests were performed using IBM SPSS statistics 20 (IBM Corp.).

RESULTS

Baseline patient characteristics. Twenty-nine patients with RA without clinical arthritis during or after treatment were included in our study (Table 1). Seventeen of 29 patients (59%) were female with a mean (SD) age of 59 (12) years. Mean (SD) disease duration was 9 (5) years. The DAS44 of all 29 included patients were low [mean (SD) = 0.8 (0.3)]. When checking with the newly published 2011 ACR/EULAR Boolean remission criteria[2], all but 2 patients fulfilled these criteria: 1 patient had a visual analog scale of 2 (measured on a scale from 0–10) and 1 patient had a C-reactive protein of 2 mg/dl. Patients received various medication regimens, because no treatment limitations were applied. Seven patients (24%) did not receive any treatment with DMARD, biologics, or prednisolone at the time of PET/MRI scanning.

Clinical followup. Cumulative occurrence of a flare was reported in 3 (10%), 8 (28%), 15 (52%), and 17 (59%) patients within 0.5, 1, 2, and 3 years from baseline PET/MRI scanning, respectively.

During followup, antirheumatic medication dosage was reduced in 7 patients during the 3-year clinical followup period. Of those 7 patients, 3 (43%) developed a flare. Thirteen of 22 (59%) patients developed a flare with a stable medication regimen.

PET evidence of subclinical inflammation at baseline. PET scan analysis revealed that 16 patients (55%) with RA without clinical arthritis had at least 1 (range 1–17) PET-positive joint at baseline (Figure 1). Moreover, 7 positive PET scans (24%) showed moderate to high tracer uptake (score ≥ 2) in at least 1 joint and at most in 7 joints. The median (IQR) PET-positive joint count was 1.0 (0–2) and the median (IQR) cumulative PET score was 1.0 (0–2; range 0–24). At a joint level, 50 of 638 (8%) investigated joints were PET positive, with 22 PET-positive joints showing moderate to intense uptake (score 2–3) of (R)-^{11}C-PK11195.

Table 1. Patient baseline characteristics.

Baseline Characteristics	n = 29
Female, n (%)	17 (59)
Age, yrs, mean ± SD	59 ± 12
Disease duration, yrs, mean ± SD	9 ± 5
44–swollen joint count	0
44–tender joint count	0
2011 ACR/EULAR remission, n (%)	27 (93)
VAS general health, mean ± SD	5 ± 4
ESR, median (IQR)	7 (6–17)
CRP, median (IQR)	2 (1–4)
Treatment, n (%)	
MTX monotherapy	9 (31)
SSZ monotherapy	1 (3)
HCQ monotherapy	2 (7)
MTX, SSZ, HCQ combination therapy	1 (3)
Anti-TNF + MTX	9 (31)
Additional oral prednisolone (maximal dosage 7.5 mg/day)	3 (10)
No therapy	7 (24)

ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; ESR: erythrocyte sedimentation rate; IQR: interquartile range; CRP: C-reactive protein; MTX: methotrexate, SSZ: sulfasalazine; HCQ: hydroxychloroquine; TNF: tumor necrosis factor; VAS: visual analog scale.

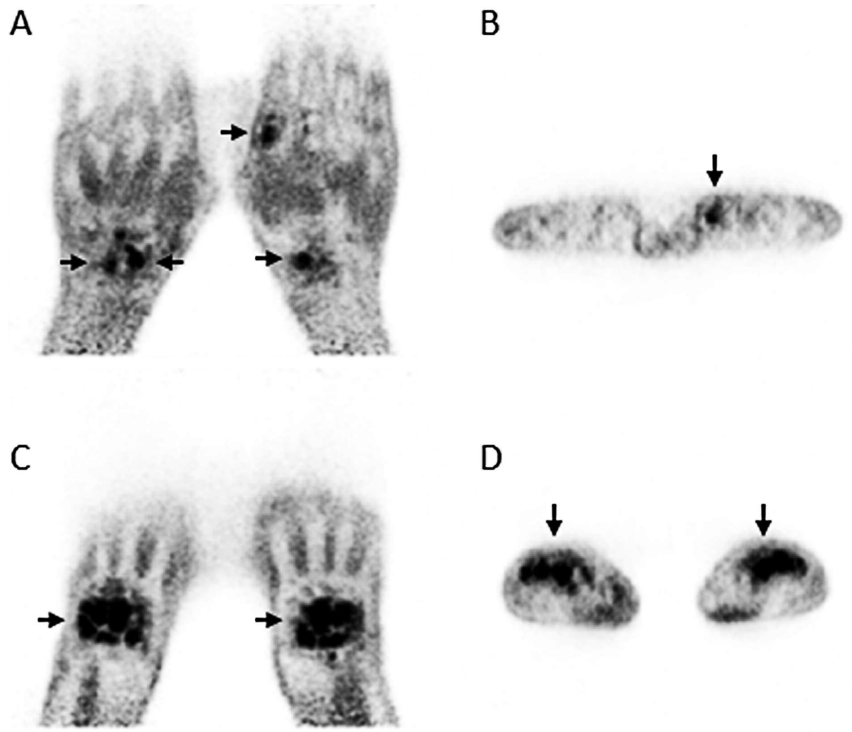

Figure 1. (R)-^{11}C-PK11195 PET scans. Examples of coronal (A and C) and transverse (B and D) (R)-^{11}C-PK11195 PET scans of a patient with RA without clinical synovitis. Increased uptake of the macrophage targeting PET tracer (R)-^{11}C-PK11195 appears as a black hotspot (arrows) in MCP (A and B) and wrist joints (A–D). PET: positron emission tomography; MCP: metacarpophalangeal; RA: rheumatoid arthritis.

PET outcome related to development of flare. Sixty-nine percent of patients (11/16) with a positive PET at baseline developed a flare during followup. From these patients, 9 of 11 developed a flare in the hand/wrist region (i.e., the region of the PET scan). Forty-six percent (6/13) of patients with a negative PET also developed a flare, although in 2 patients the flare was localized outside the hands and/or wrists.

All 3 patients who developed a flare within 6 months had a positive (R)-^{11}C-PK11195 PET scan with cumulative PET scores ranging from 6 to 24 [and with a moderate tracer uptake (i.e., score 2) in 3–7 joints; Figure 2A]. Progressively lower cumulative PET scores were found for patients who developed a flare after 6 months from PET scanning (n = 14). Importantly, no patients with a negative PET developed a flare within 6 months (Figure 2A).

Median (IQR) cumulative PET scores of patients with a flare (n = 17) were significantly higher compared to those without a flare [n = 12; 2.0 (0–4.5) vs 0 (0–1.0), $p < 0.05$; Figure 3, left panel]. Patients with a flare also had a higher median (IQR) PET-positive joint count than did those without a flare [1.0 (0–2.0) vs 0 (0–1.0), $p < 0.05$].

At joint level, no correlation was found between PET positivity and the site of flare.

PET and clinical outcome in relation to MRI. Of all PET-positive patients (n = 15), 13 also had a positive MRI scan, thus showing a high proportion of positive agreement (87%) at a patient level. However, it was remarkable that of all PET-negative patients (n = 13), a majority (n = 10, 77%) still had positive MRI results (Figure 4).

Comparison of PET and MRI results related to clinical outcome demonstrated that patients (n = 3) with the highest cumulative PET scores and development of a flare within 6 months (Figure 2A) also displayed the highest cumulative MRI scores (Figure 2B). Discordant findings between PET and MRI were, however, demonstrated in 7/13 patients (54%) who developed a flare later during followup (Figure 2A and 2B).

Based on dichotomous outcome of PET and MRI at patient level, no additional value of MRI to PET or vice versa was present with regard to prediction of flare (Figure 4). However, when cumulative scores of PET and MRI were observed in relation to development of flare, it was shown that cumulative PET scores differed significantly between the group with and without a flare (see above), while no significant difference was found for cumulative MRI scores [median (IQR) 10.0 (3.0–19.0) vs 3.0 (0.5–16.8), respectively; Figure 3, middle panel]. Examination of MRI RAMRIS scores of the dominant hand did not change this

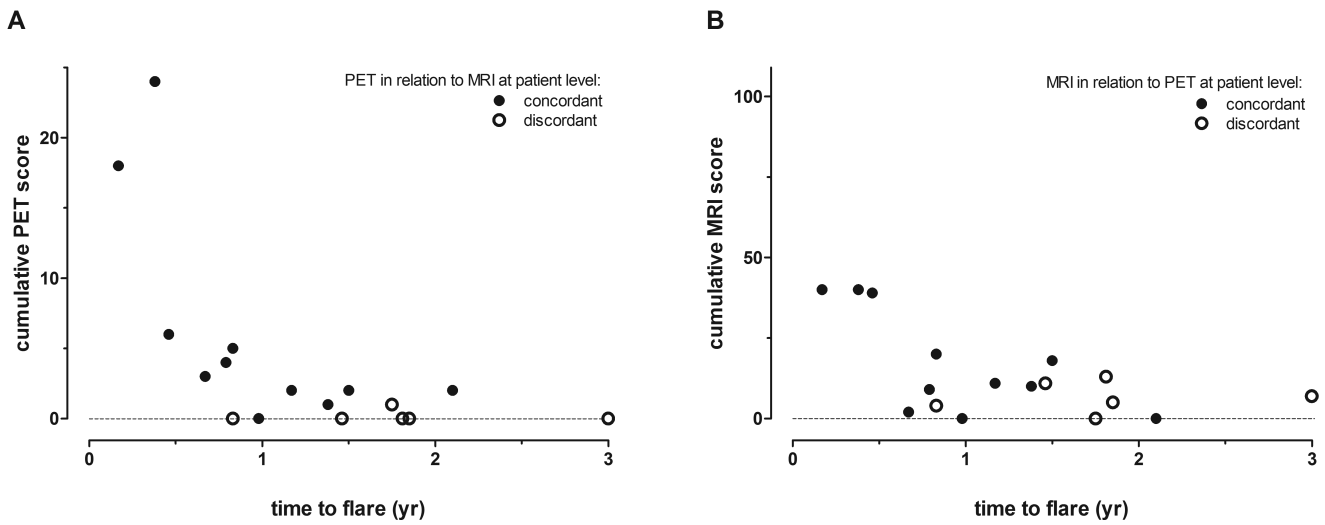

Figure 2. Patient cumulative PET and MRI scores. Cumulative (R)-^{11}C-PK11195 PET (A) and MRI (B) scores of remission patients with RA in relation to time (in years) to flare. Patients are indicated by individual symbols; black and white dots represent patients with, respectively, concordant and discordant PET and MRI findings at a patient level. The y-axes, representing PET and MRI cumulative scores, were scaled to the maximum possible score. PET: positron emission tomography; MRI: magnetic resonance imaging.

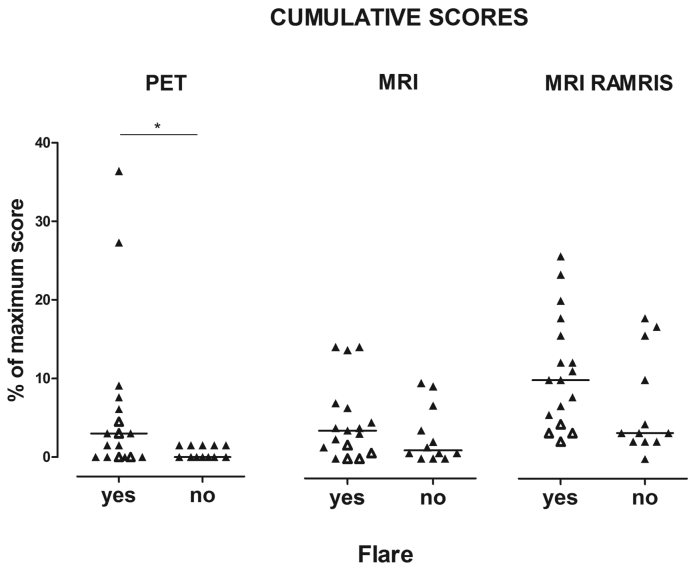

Figure 3. PET, MRI, and MRI RAMRIS scores of patients with and without a flare. Comparison of cumulative PET scores of both hands (left panel), cumulative MRI scores of both hands (middle panel), and cumulative MRI RAMRIS scores of the dominant hand (right panel) of patients with and without a flare. Absolute cumulative PET, MRI, and MRI RAMRIS scores were recalculated as percentage of the maximum possible cumulative score (66, 288, and 90, respectively). Horizontal lines represent median scores. Open symbols represent patients with a flare outside hands/wrist, yes = flare, and no = no flare. *$p < 0.05$. PET: positron emission tomography; MRI: magnetic resonance imaging; RAMRIS: Rheumatoid Arthritis Magnetic Resonance Imaging Scoring.

result; moreover, at a dichotomous level, all but 1 patient had a positive MRI at patient level if MRI RAMRIS scores were used (Figure 3, right panel).

Exclusion of 7 patients who received a dose reduction of antirheumatic medication during followup from our analysis demonstrated that cumulative PET scores were still significantly different between the flare and no-flare group in contrast to cumulative MRI and cumulative MRI RAMRIS scores (data not shown). Moreover, median (IQR) cumulative PET and MRI scores of the group with a dose

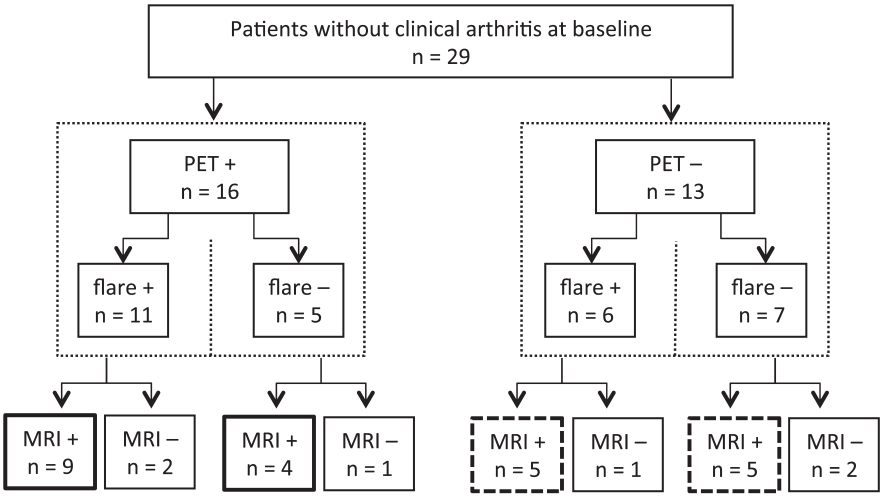

Figure 4. Baseline dichotomous imaging results in relation to development of flare at patient level. Bold box indicates PET-positive patients who also had positive MRI findings. Dotted box indicates PET-negative patients who still had positive MRI findings. Using dichotomous MRI and PET results, MRI did not have an additive value to PET with regard to prediction of flare, and PET did not have additive value to MRI (results not shown). PET: positron emission tomography; MRI: magnetic resonance imaging.

reduction versus the group with stable medication did not differ significantly [PET 1.0 (0.0–1.0) vs 1.0 (0–2.3), p = 0.7; MRI 6 (2–19) vs 8 (1.5–18.5), p = 0.8].

Finally, similar to PET, no relation between MRI and clinical outcome was present at joint level.

DISCUSSION

Our explorative study showed that enhanced uptake of (R)-^{11}C-PK11195 as visualized by PET can be detected in hands and/or wrists of treated patients with RA without clinical arthritis, suggesting the presence of activated synovial macrophages. Further, patients who developed a flare during followup had higher cumulative PET scores than those who did not. Patients with the highest cumulative PET scores (≥ 6) already developed a flare within 6 months. In contrast, patients who did not develop a flare within the followup period had consistently low cumulative PET scores (≤ 1). These findings may potentially contribute to treatment decisions during remission of RA.

Initially, our present study was designed to explore the potential of (R)-^{11}C-PK11195 PET in the detection of subclinical joint inflammation in patients with RA without clinical arthritis. To put the PET data in perspective, our study protocol also comprised the more widely explored contrast-enhanced MRI in addition to PET. Although a direct comparison of the level of cumulative PET and MRI scores was not feasible because of different scoring methods, for each imaging modality, cumulative scores could be compared between flare and no-flare patient groups. This revealed a significant difference in cumulative PET scores, but not cumulative MRI scores, between patients with and without a flare. The latter could mainly be explained by the wide range of cumulative MRI scores that was present in the subgroup that did not develop a flare. This comparison suggested that PET has potential value compared to MRI with regard to specificity. On the other hand, 5/6 patients with a negative PET and development of flare did have a positive MRI scan, implying that the sensitivity level of MRI may add to PET. Our current study was not designed as a prospective comparative trial between (R)-^{11}C-PK11195 and contrast-enhanced MRI, and numbers in the subgroups were small. This allows only preliminary conclusions, but these interesting observations warrant further confirmation in larger cohorts. Differences in performance between PET and MRI are most likely related to imaging of molecular pathophysiology [in our study at the level of macrophages (PET)] versus imaging of anatomical changes of synovial tissue and bone marrow, as well as local perfusion status (MRI). In this perspective, the recently introduced hybrid PET-MRI technique may become a valuable imaging technique for detection of subclinical disease activity, combining the strengths of both techniques. For future clinical applications, one should also acknowledge the patients' exposure to radiation by PET scanning. However, the radiation burden of the (R)-^{11}C-PK11195 is only 2 mSv (because of rapid decay with a half-life of 20 min of C-11 tracers), which is equal to the yearly natural background radiation. On the other hand, this short half-life prevents wide distribution of (R)-^{11}C-PK11195 from its production site. Future studies with longer-living TSPO ligands could therefore be useful. One candidate may be the tracer ^{18}F-DPA-714, which has a half-life of 109 min and shows

promise in preclinical work in an arthritic rat model performed by our group[30].

In line with our results, a high level of positive findings on MRI for both synovitis and bone marrow edema in patients with RA remission has been consistently found in other studies[8,11]. Recent MRI studies, however, indicate that cutoff levels for cumulative MRI scores will probably be required for identification of those patients who will most likely develop (radiographic) progression of disease[31]. Similarly, in our study, the use of cumulative PET and MRI scores also turned out to be more informative than dichotomous PET and MRI outcome. With regard to radiological outcome in relation to PET and MRI, we could not draw final conclusions, because available radiographs of the hands of a subgroup of patients at 1-year followup showed only minimal radiological progression (data not shown). Longterm radiological outcome should be included in future studies to further evaluate predictive power of PET in remission and low disease activity states of RA.

A limitation of our work is the collection of clinical followup data by screening of medical chart reports describing clinical joint examinations by treating rheumatologists, instead of structural predefined clinical assessment. We have, however, applied flare definitions that largely preclude single observations of arthritis of 1 joint at only 1 occasion. Clinical judgments were such that evident flaring was noticed by the managing clinicians. Subtle arthritis may have been missed, though, which may have led to underestimation of the predictive value of MRI. To consolidate clinical observations, an additional 44-joint examination was performed by a blinded clinical investigator at 3 years of followup. With the exception of 1 (who developed clinical arthritis at 3 yrs), we confirmed the "no flare" status in the group of 13 patients of whom no flare was reported in the chart, supporting the validity of these clinical findings. The latter confirmation is particularly relevant in view of the demonstrated promising value of PET concerning specificity.

Flexibility in treatment regimen during clinical followup did not affect observed differences of PET and MRI outcome between flare and no-flare groups, as reported in the results section.

Another limitation of our study is confinement of the scanning region to the hands and wrists, which could have led to the missing of subclinical arthritis in other joints. However, in our study, the majority of patients developed a flare in hands and/or wrists. Nevertheless, future studies should investigate whether whole body assessment has additive value to scanning of only hands/wrists.

Our prospective explorative study showed that PET could visualize enhanced uptake of the macrophage targeting tracer (R)-^{11}C-PK11195 in hand and/or wrist joints of patients with RA without clinical arthritis during and after treatment.

A preliminary comparison between (R)-^{11}C-PK11195 PET and MRI showed that both may be equally associated with development of short-term flare in RA remission and could therefore be of help in treatment decisions in this group of patients. However, (R)-^{11}C-PK11195 PET may have added diagnostic specificity value because of consistently low scores in the "no flare" subgroup. Confirmation of these results is warranted in larger cohorts.

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