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## Rheumatoid arthritis: Nuclear Medicine state-of-the-art imaging

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### Abstract

Rheumatoid arthritis (RA) is an autoimmune disease, which is associated with systemic and chronic inflammation of the joints, resulting in synovitis and pannus formation. For several decades, the assessment of RA has been limited to conventional radiography, assisting in the diagnosis and monitoring of disease. Nevertheless, conventional radiography has poor sensitivity in the detection of the inflammatory process that happens in the initial stages of RA. In the past years, new drugs that significantly decrease the progression of RA have allowed a more efficient treatment. Nuclear Medicine provides functional assessment of physiological processes and therefore has significant potential for timely diagnosis and adequate follow-up of RA. Several single photon emission computed tomography (SPECT) and positron emission tomography (PET) radiopharmaceuti-

cals have been developed and applied in this field. The use of hybrid imaging, which permits computed tomography (CT) and nuclear medicine data to be acquired and fused, has increased even more the diagnostic accuracy of Nuclear Medicine by providing anatomical localization in SPECT/CT and PET/CT studies. More recently, fusion of PET with magnetic resonance imaging (PET/MRI) was introduced in some centers and demonstrated great potential. In this article, we will review studies that have been published using Nuclear Medicine for RA and examine key topics in the area.

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**Key words:** Rheumatoid arthritis; Nuclear medicine; Scintigraphy; Single photon emission computed tomography; Positron emission tomography

**Core tip:** In recent years, the use of nuclear medicine to characterize and diagnose infectious and inflammatory diseases has been rapidly increasing. In the case of rheumatoid arthritis (RA), the success of treatment requires improvement of early diagnosis and assessment of response to anti-inflammatory therapy. In this setting, Nuclear Medicine may be valuable in the assessment of early inflammatory activity in RA, foreseeing and monitoring response to treatment, and allowing the selection of optimal treatments for each patient. The development of new radiopharmaceuticals and hybrid imaging technologies may improve the potential of molecular imaging in the field.

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## INTRODUCTION

For many years, the evaluation of rheumatoid arthritis (RA) has been restricted to conventional radiography, helping to establish the diagnosis and, subsequently, to monitor the progression of disease. However, this modality doesn't have good sensitivity in identifying the inflammatory process that occurs in the initial stages of the disease. In the past 20 years, new drugs (particularly biological agents) that greatly reduce the progression of RA have allowed a more efficient treatment. Therefore, an early diagnosis and an adequate follow-up of the disease have become major challenges for Rheumatology and Radiology, and better results can only be achieved if technologies from both specialties are developed together.

New imaging systems have been presented in the past years and digital technologies significantly transformed clinical practice. Here, we will review the different studies that have been published using nuclear medicine for evaluation of RA and discuss important aspects in the area.

## CONVENTIONAL NUCLEAR MEDICINE

Conventional nuclear medicine techniques are divided basically into two-dimensional planar scans and three-dimensional single photon emission computed tomography (SPECT), which permits reconstruction of images in sagittal, coronal and axial planes<sup>[1-3]</sup>. SPECT images allow improved localization of the site of uptake (*e.g.*, for differentiating involvement of the facets or pedicle of a vertebra), and increases sensitivity and specificity<sup>[1-3]</sup>. Hybrid SPECT/computed tomography (CT) imaging, which allows morphological and functional data to be acquired and fused, increases even more the diagnostic accuracy of Nuclear Medicine studies because it provides anatomical localization of SPECT findings<sup>[4]</sup>.

Different radionuclides, including Technetium-99m (<sup>99m</sup>Tc), Gallium-67 (<sup>67</sup>Ga), Indium-111 (<sup>111</sup>In) and Iodine-123 (<sup>123</sup>I) have been used in studies for RA and will be reviewed in the following sections.

### <sup>99m</sup>Tc-labeled diphosphonates

Amongst the different radionuclides available, <sup>99m</sup>Tc is presently the most commonly used<sup>[3,5]</sup>. For the evaluation of bone diseases, there are different radiopharmaceuticals available including <sup>99m</sup>Tc labeled hydroxy methylene diphosphonate (HDP), dicarboxy propane diphosphonate (DPD) and methylene-diphosphonate (MDP), with the latter being the most commonly used<sup>[1-3]</sup>. After intravenous injection, <sup>99m</sup>Tc-MDP circulates in the vascular system, then equilibrates to the extravascular space and, subsequently, accumulates in the bone. These three phases may be evaluated in a bone scintigraphy, which has high sensitivity but low specificity. In many cases, distinction between degenerative, inflammatory and metastatic bone processes may be difficult<sup>[1-3,6]</sup>. In RA, bone scintigraphy has a certain degree of usefulness and may allow identification of arthritic joints<sup>[7,8]</sup>. However, planar scintigraphy

and SPECT have the limited spatial resolution in comparison to radiography and magnetic resonance imaging (MRI)<sup>[3,5]</sup>.

Bachkaus *et al*<sup>[6]</sup> performed a prospective study comparing clinical evaluation, conventional radiography, ultrasound, three-phase <sup>99m</sup>Tc-MDP bone scintigraphy and MRI in 60 patients with different types of arthritis including RA, arthritis related to connective tissue disease and spondylarthropathy. They found that clinical assessment, scintigraphy, ultrasound and MRI were more sensitive than radiography in identifying inflammatory processes and destructive joint lesions. However, scintigraphy had limited specificity.

Recently, in an attempt to improve the specificity of SPECT images, Ostendorf *et al*<sup>[9]</sup> studied the application of a multipinhole SPECT (MPH-SPECT), originally created for small animal imaging<sup>[10]</sup>. Six human subjects were studied after injection of <sup>99m</sup>Tc-DPD: 3 with established RA, 1 with early RA, 1 with osteoarthritis (OA) and 1 healthy volunteer. The authors reported better identification of anatomic landmarks with MPH-SPECT in contrast to planar scintigraphies, but comparison with other methods such as MRI was limited.

In a second study by the same group, the clinically dominant hands of 13 subjects with initial RA, nine with initial OA and five control subjects were evaluated by MPH-SPECT and skeletal scintigraphy. MRI was carried out in RA subjects, and these images were later fused with MPH-SPECT. Bone scintigraphy identified 26 articulations with augmented uptake while MPH-SPECT detected 80 joints. MPH-SPECT indicated a central tracer uptake in RA (10 out of 13 patients) and an eccentric pattern in OA (7 out of 9 patients). Uptake in MPH-SPECT matched areas of marrow edema and destruction in MRI in 11 out of 13 patients.

Buchbender *et al*<sup>[11]</sup> compared 3 tesla MRI with <sup>99m</sup>Tc-DPD scintigraphies using MPH-SPECT in 10 early RA patients. Visual and region of interest (ROI) analyses of MPH-SPECT images were carried out. The authors reported that MPH-SPECT detected higher rates of inflammatory bone involvement compared to MRI.

### <sup>67</sup>Ga-citrate

The accumulation of <sup>67</sup>Ga-citrate into inflammatory is complex and involves different mechanisms. It binds to transferrin and suffers extravasation in areas of inflammation where vascular permeability is increased<sup>[12,13]</sup>. Moreover, <sup>67</sup>Ga suffers cross-chelation to lactoferrin, a protein released which is taken up by macrophages and also binds to siderophores, low-molecular-weight products of bacteria<sup>[12,13]</sup>.

Even though <sup>67</sup>Ga-citrate scintigraphy has good sensitivity detection of inflammation and has been used in the evaluation of RA<sup>[3,13-15]</sup>, there are numerous drawbacks with this technique. <sup>67</sup>Ga scintigraphy leads to relatively elevated radiation burden because of its physical half-life and high-energy gamma radiation (91-393 keV)<sup>[16]</sup>. It also has elevated background activity and slower imaging times. Additionally, it cannot precisely differentiate in-

flammation from infection or neoplasias<sup>[13]</sup>.

### <sup>99m</sup>Tc and <sup>111</sup>In-labeled leukocytes

Leukocytes may be labeled with <sup>99m</sup>Tc or <sup>111</sup>In-oxine for detection of inflammatory and infectious diseases<sup>[3,17-20]</sup>. Al-Janabi *et al.*<sup>[21]</sup> labeled leukocytes with <sup>99m</sup>Tc in subjects with RA and found a 50%-80% decrease in leukocyte uptake after local steroid injection into eight out of nine painful knees, which showed clinical response. Gaál *et al.*<sup>[22]</sup> performed <sup>99m</sup>Tc-hexamethylpropylene amine oxime (<sup>99m</sup>Tc-HMPAO) labeled leukocyte scintigraphy in 21 patients with RA. A significant association was seen between the uptake in hands and feet and clinical evaluation. Thurlings *et al.*<sup>[23]</sup> performed two scintigraphies after injection of <sup>99m</sup>Tc-HMPAO labeled monocytes in eight RA patients, with a two-week interval. Arthroscopic biopsies were performed one day after the second scintigraphy and synovial macrophage infiltration was evaluated by immunohistochemical staining. The number of scintigraphically positive joints was significantly associated with the number of activated macrophages in the synovium.

### <sup>99m</sup>Tc-labeled ciprofloxacin

Appelboom *et al.*<sup>[24]</sup> investigated the use of <sup>99m</sup>Tc labeled ciprofloxacin (Infecton scintigraphy) in 106 patients, 17 of them with RA. Subjects received an intravenous injection of <sup>99m</sup>Tc-ciprofloxacin and whole body scans were acquired after 4 h. Augmented uptake was seen in 12 patients with RA. Association between clinically inflamed joints and articular <sup>99m</sup>Tc-ciprofloxacin uptake was observed. The authors concluded that the radiotracer was not specific for infection and could potentially identify the presence of inflammation in joints and monitor their response to treatment.

### <sup>99m</sup>Tc-labeled human immunoglobulin G

Labeling polyclonal human immunoglobulin G (HIG) with <sup>99m</sup>Tc allows evaluation of inflammation and infection. Different groups have suggested that these exams may have higher sensitivity than clinical assessment, bone scintigraphy and labeled leukocyte scintigraphy<sup>[25,26]</sup>. However, similar to radiotracers like <sup>67</sup>Ga, the exam has limited specificity.

### <sup>99m</sup>Tc and <sup>111</sup>In-anti-E-selectin

Chapman *et al.*<sup>[27]</sup> evaluated the biodistribution of <sup>111</sup>In-labeled anti-E-selectin monoclonal antibodies in 14 subjects with RA and compared it with <sup>111</sup>In-labeled polyclonal HIG in 6 of these patients. <sup>111</sup>In-anti-E-selectin resulted in better sensitivity and image intensity and more focal localization in synovium.

The same group published another study where they used <sup>111</sup>In-anti-E-selectin and <sup>99m</sup>Tc-labeled polyclonal HIG in 11 patients with RA<sup>[28]</sup>. Scintigraphic images were compared with clinical scores. The authors reported that <sup>111</sup>In-anti-E-selectin had greater sensitivity and specificity than <sup>99m</sup>Tc-HIG. However, the necessity of performing 24 h images with <sup>111</sup>In-anti-E-selectin led to the devel-

opment of a <sup>99m</sup>Tc-labeled tracer<sup>[29]</sup>. In this study, the authors performed scintigraphies 4 h and 20-24 h after <sup>111</sup>In- or <sup>99m</sup>Tc-anti-E-selectin injection in a group of 10 patients with RA. They concluded that they led to similar diagnostic accuracy, what favored the use of the <sup>99m</sup>Tc-labeled tracer. In another group of 16 RA patients, <sup>99m</sup>Tc-anti-E-selectin was compared with <sup>99m</sup>Tc-HDP 4h after injection. Although <sup>99m</sup>Tc-anti-E-selectin seemed to have *in vivo* instability, as indicated by thyroidal and intestinal uptake, <sup>99m</sup>Tc-anti-E-selectin was better than <sup>99m</sup>Tc-HDP (88% *vs* 57%) in terms of accuracy. Inactive or normal joints didn't show uptake of <sup>99m</sup>Tc-anti-E-selectin.

### <sup>111</sup>In-octreotide

Vanhagen *et al.*<sup>[30]</sup> studied the articulations of 14 subjects with ongoing RA, 4 with intense OA, and 30 controls. The somatostatin analog <sup>125</sup>I-Tyr3-octreotide was used for *in vitro* somatostatin receptor autoradiography and the somatostatin analog <sup>111</sup>In-DTPA-D-Phe1-octreotide was used for scintigraphy. A total of 76% of tender and of augmented joints of the subjects with RA were identified by nuclear medicine scans. The authors found that joint uptake was associated with the amount of pain and swelling. *In vitro* autoradiography of the synovial membranes indicated somatostatin receptors in 2 of the RA patients. In subjects with OA, joint uptake was considerably poorer than in subjects with RA, while the ones of control subjects didn't exhibit uptake.

### <sup>99m</sup>Tc-anti-CD3

Marcus *et al.*<sup>[31]</sup> studied the biodistribution of a <sup>99m</sup>Tc-labeled murine monoclonal antibody (Muromonab, Orthoclone OKT3®), specific for T lymphocyte glycoprotein CD3 receptor. Seven patients with RA and two with psoriatic arthritis were included. Scintigraphies of the whole-body and of the articulations were carried out. All joints with intermediate to intense pain showed intermediate to high uptake, while all asymptomatic joints and joints with mild or minimal pain had normal images. Of note, two patients had side effects (shaking chills and neck pain) after <sup>99m</sup>Tc-OKT-3 injection.

Our group of research developed another technique for labeling OKT3 with <sup>99m</sup>Tc and also investigated its use to evaluate disease activity in subjects with RA. A total of 38 patients with RA functional classes II and III according to American College of Rheumatology criteria were evaluated<sup>[32]</sup>. Planar anterior scans of the patients' metacarpophalangeal and interphalangeal joints, shoulders, elbows, wrists and knees were carried out 1 h and 3 h after the infusion of <sup>99m</sup>Tc-OKT3. Significant association ( $P < 0.05$ ) was found between the <sup>99m</sup>Tc-OKT3 uptake and swollen or tender joints and the visual analogue scale. It was possible to distinguish subjects in remission from subjects with active synovitis. On the other hand, no association was seen between <sup>99m</sup>Tc-OKT3 uptake and the patients' duration of disease, gender and age or erythrocyte sedimentation rate.

In a continuation of the previous report, we have

studied 1232 joints from 44 patients with RA were evaluated 1 h and 3 h after injection of anti-CD3 antibody labeled with  $^{99m}\text{Tc}$  and compared with another 812 joints from 33 patients with juvenile idiopathic arthritis (JIA), OA or gouty arthritis (GA)<sup>[33]</sup>. RA and JIA showed high uptake at the first scan, which augmented after 3 h. In OA, uptake was minimal or absent. Therefore, it was possible to distinguish RA and JIA from OA and GA. However, it was not possible to distinguish subjects with RA in remission from those with OA.

#### $^{99m}\text{Tc}$ -anti-CD4

Becket *et al.*<sup>[34]</sup> performed three-phase bone scans with  $^{99m}\text{Tc}$ -HDP and scintigraphies with an anti-CD4 antibody named MAX.16H5 labeled with  $^{99m}\text{Tc}$ . Six patients with RA were included prospectively and five of them received  $^{99m}\text{Tc}$ -anti-CD4 scans after 1.5 h, 4 h and 24 h. In all patients, affected joints could be distinctively imaged at as early as 1.5 h. The authors reported that uptake in affected joints was associated with clinical signs and early  $^{99m}\text{Tc}$ -MDP weakly uptake. However, it was not clear if late uptake of the radiotracer differed from control immunoglobulins.

To evaluate this aspect, the same group later included eight patients with severe, active RA to perform scintigraphies with  $^{99m}\text{Tc}$ -labeled anti-CD4 or polyclonal HIG, with five of them receiving both radiotracers<sup>[35]</sup>. Scintigraphies of the whole-body and of the joints were carried out after 1, 4 and 24 h. The authors found that  $^{99m}\text{Tc}$ -anti-CD4 had higher target-to-background ratio in knee and elbow joints, suggesting higher specificity than  $^{99m}\text{Tc}$ -HIG.

#### $^{99m}\text{Tc}$ -anti-CD20

Malviya *et al.*<sup>[36]</sup> labeled Rituximab, an anti-CD20 antibody (MabThera®), with  $^{99m}\text{Tc}$  in 20 patients with chronic inflammatory diseases and acquired scintigraphies after 6 h and 20 h. Five of the patients had RA and presented uptake of the radiotracer in known lesioned joints. Nonetheless, such uptake was variable and not all patients showed uptake in each clinically positive joint.

#### $^{99m}\text{Tc}$ -anti-tumor necrosis factor-alpha

Chianelli *et al.*<sup>[37]</sup> labeled Infliximab (Remicade®), a chimeric mouse/human anti-tumor necrosis factor alpha (anti-TNF-alpha) antibody, with  $^{99m}\text{Tc}$  and included seven RA patients eligible to receive intra-articular Infliximab therapy for scintigraphic evaluation previously and 3 mo following the therapy. Planar scans of the joints were carried out 3, 6 and 24 h after intravenous infusion of  $^{99m}\text{Tc}$ -Infliximab. Post-treatment scans indicated that the uptake disappeared in 1 joint, was reduced considerably in 2, was faintly in 4 and remained unchanged in 2. The authors suggested  $^{99m}\text{Tc}$ -Infliximab could potentially aid in the choice of those subjects who would profit most from treatment with unlabeled Infliximab and provide a more objective assessment of immunotherapy efficacy.

A study from our group of research compared whole

body and hand/wrist scintigraphies after injection of  $^{99m}\text{Tc}$ -anti-TNF- $\alpha$  with clinical examination and MRI of wrists joints and hands in subjects with active RA<sup>[38]</sup>. Eight subjects with active RA and one healthy volunteer were included. With MRI considered as the gold standard, the sensitivity and specificity of scintigraphy was 89.9% and 97.3%, respectively, while pain and edema had sensitivity of 65.3% and 59.2% and specificity of 75.2% and 95.3%, respectively.

#### $^{123}\text{I}$ -IL-1 receptor antagonists

Barrera *et al.*<sup>[39]</sup> studied the biodistribution of  $^{123}\text{I}$  labeled interleukin-1 receptor antagonist (IL-1ra) in four subjects with RA. A comparison of scintigraphies acquired with  $^{123}\text{I}$ -IL-1ra and those acquired with a non-specific radiopharmaceutical was made. Although the authors found that labelled IL-1ra allowed the identification of synovial disease in subjects with RA this process did not seem to occur by specific binding.

## POSITRON EMISSION TOMOGRAPHY

The radionuclides that have been used for Positron Emission Tomography (PET) include fluorine-18 ( $^{18}\text{F}$ ), carbon-11 ( $^{11}\text{C}$ ) and iodine-124 ( $^{124}\text{I}$ ). PET has two to three times higher spatial resolution than SPECT and permits quantification of standardized uptake value (SUV)<sup>[40-42]</sup>. In the following sections the studies that used PET for RA monitoring are reviewed.

#### $^{18}\text{F}$ -fluoro-D-glucose

2-deoxy-2- $^{18}\text{F}$  fluoro-D-glucose ( $^{18}\text{F}$ -FDG) allows evaluation of tissue metabolism.  $^{18}\text{F}$ -FDG accumulation in inflammatory and infectious diseases is based on its increased uptake by polymorphonuclear leukocytes, which adopt glucose after becoming activated. The transportation of  $^{18}\text{F}$ -FDG is intermediated by glucose transporters (GLUT), which are also to a higher amount present on the cell membrane of inflammatory and infectious cells. RA is an autoimmune disease, which is associated with systemic and chronic inflammation of the joints, resulting in synovitis and pannus formation, both leading to increased  $^{18}\text{F}$ -FDG uptake.

Polisson *et al.*<sup>[43]</sup> published a seminal report where  $^{18}\text{F}$ -FDG PET and MRI were carried out in 2 RA patients with active synovitis in the carpus at baseline and after 14 wk of treatment. In comparison with baseline, there was marked improvement in clinical parameters and decrease in synovial volume measured by MRI and  $^{18}\text{F}$ -FDG uptake measured by PET.

The same group published later another study where  $^{18}\text{F}$ -FDG PET and gadolinium-enhanced MRI of the wrist were carried out prospectively in 12 subjects under anti-inflammatory treatment in different moments: without drugs for 2 wk and after 2 and 12 wk of treatment<sup>[44]</sup>. They found that MRI and  $^{18}\text{F}$ -FDG PET were strongly correlated with clinical findings in wrists, and concluded that these techniques permitted quantification of altera-

tions in joint inflammation. In addition to these reports, other articles have indicated the capability of  $^{18}\text{F}$ -FDG PET to identify alterations in disease activity, but few have shown it can foretell clinical results<sup>[45,46]</sup>.

Nonetheless, one of the most important breakthroughs in the field of Nuclear Medicine has been the advent of PET/CT hybrid imaging, which allows concomitant acquisition of morphologic and functional information, increasing both sensitivity and specificity of findings. Initial case studies suggested that  $^{18}\text{F}$ -FDG PET/CT correctly identifies articular and extra-articular inflammatory areas<sup>[47-49]</sup>. Kubota *et al.*<sup>[50]</sup> performed  $^{18}\text{F}$ -FDG PET/CT in 18 subjects with RA and evaluated uptake in the atlanto-axial, shoulder, elbow, wrist, carpal, knee and hip joints and in axillary lymph nodes. The total uptake score for all joints was significantly associated with C-reactive protein level. Furthermore,  $^{18}\text{F}$ -FDG uptake score of painful/swollen joints were greater than not painful/swollen joints and significantly distinct between subjects in remission and those with active inflammation. Roivainen *et al.*<sup>[51]</sup> studied 17 subjects with active RA that started to receive disease-modifying antirheumatic drugs. Disease activity was clinically evaluated at screening, at baseline and after 2, 4, 8 and 12 wk of therapy, while  $^{18}\text{F}$ -FDG PET/CT of all joints was carried out at baseline and after 2 and 4 wk of therapy.  $^{18}\text{F}$ -FDG maximum SUV decreased in 76% and 81% at weeks 2 and 4 in comparison to baseline. The percentage of decline in  $^{18}\text{F}$ -FDG activity was associated with disease activity at week 12 and with variations in C-reactive protein levels and erythrocyte sedimentation rate.

More recently, fusion of PET and MRI has been developed. Chaudhari *et al.*<sup>[52]</sup> performed an extremity  $^{18}\text{F}$ -FDG PET/CT immediately after MRI at baseline and 5 wk after TNF-alpha inhibitor therapy in a 57-year-old female with RA. CT was later used for PET/MRI fusion. The authors reported that PET uptake decreased significantly in the synovium and at sites of erosions and clinical exam at 3 mo corroborated a positive response to therapy. Then, Miese *et al.*<sup>[53]</sup> reported on the first hybrid hand PET/MRI in initial RA, demonstrating augmented  $^{18}\text{F}$ -FDG uptake occurred in synovitis.

### $^{11}\text{C}$ -choline

Roivainen *et al.*<sup>[54]</sup> included 10 subjects with inflammatory disorders of the joints, two of them with RA, in a study that compared  $^{11}\text{C}$ -choline and  $^{18}\text{F}$ -FDG PET with contrast-enhanced MRI. The authors found that the uptake of  $^{18}\text{F}$ -FDG as well as  $^{11}\text{C}$ -choline had good correlation with synovial volume measured in MRI and suggested  $^{11}\text{C}$ -choline could be a promising radiotracer for quantitative assessment of disease activity.

### $^{11}\text{C}$ -(R)-PK11195

$^{11}\text{C}$ -(R)-PK11195 is a radiotracer that suffers macrophage binding. Van der Laken *et al.*<sup>[55]</sup> studied the knees of 11 RA patients using  $^{11}\text{C}$ -(R)-PK11195 PET imaging and arthroscopic assessment of the knee with greatest inflam-

mation in all subjects. The authors found that  $^{11}\text{C}$ -(R)-PK11195 had significantly increased uptake in inflamed joints. Moreover, uptake in non-inflamed knees of RA subjects was considerably greater than in the knees of controls, indicating the existence of subclinical RA activity.

### $^{124}\text{I}$ -anti-CD20

Tran *et al.*<sup>[56]</sup> included six patients in a study to evaluate the distribution of  $^{124}\text{I}$  labeled Rituximab. One patient was excluded due to adverse effects after injection of the unlabeled drug. Whole body PET/CT was carried out in 5 subjects at 10 min, 24 h, 48 h and 72-96 h. Evaluation was carried out based on visual analyses and correlated with disease activity. Accumulation in joints occurred only after 24 h, in 4 out of 5 patients. The authors reported that several exams had uptake in clinically normal joints while a few joints with clinical arthritis had no uptake, but no quantification or comparison with other imaging methods was performed.

## CONCLUSION

The success of RA therapy requires improvement of early diagnosis and evaluation of response to anti-inflammatory treatment. New powerful and efficient medications are now offered that can change the natural history of the disease. Molecular imaging may be useful in the evaluation of early inflammatory activity in RA, predicting and monitoring response to treatment, and allowing the selection of optimal treatments for each patient. Nuclear Medicine techniques, particularly SPECT/CT, PET/CT and PET/MRI can deliver important molecular information that may be correlated with biological therapies. However, large prospective, controlled clinical trials comparing imaging methods are still needed to improve the understanding of the potentials of Nuclear Medicine in RA.

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