ORIGINAL ARTICLE

Radionuclide imaging with human polyclonal immunoglobulin (^{99m}Tc-HIG) and bone scan in patients with rheumatoid arthritis and serum-negative polyarthritis

Gerasimou G[1], Moralidis E[1], Papanastasiou E[1], Liaros G[1], Aggelopoulou T[1], Triantafyllidou E[2], Lytras N[1], Settas L[2], Gotzamani-Psarrakou A[1]

[1]2nd Laboratory of Nuclear Medicine,University Hospital-Thessaloniki, Greece
[2]Rheumatologic Clinic, AHEPA University Hospital-Thessaloniki, Greece

Abstract

Background and aim: Rheumatoid arthritis (RA) is a chronic polyarthritic syndrome in which actively inflamed joints coexist with others being in remission. Compatible bone scan (BS) reveals joints with increased activity due to degenerative alterations, whilst scanning with human polyclonal immunoglobulin (HIG) is capable to show which of the joints present active inflammation of the synovial membrane. The aim of the study is to investigate the utility of molecular imaging with HIG in patients suffering from RA.

Patients and methods: Forty patients (9 males plus 31 females), suffering from painful polyarthritic syndrome, with a mean age 45.3±7 years and a duration of disease 18.3±4.2 months were enrolled in the study. Twenty-six of the patients were serum positive to RA factor, considered as suffering from RA, whilst fourteen of them were RA factor negatives and they were considered as patients with serum-negative polyarthritis. All patients were submitted to x-rays and ultrasound examination (US) in joints of interest, plus whole body BS with ^{99m}Tc-MDP and finally scan with ^{99m}Tc-HIG.

Results: A total of 1680 joints have been evaluated. In 6 of the patients-two with serum negative RA (252 joints), radionuclide imaging with HIG was within normal limits, despite the fact that in compatible bone scan degenerative alterations have been mentioned in 30 joints. In all these patients disease was evaluated as inactive ("arthrotic changes"). In the remaining 34 patients-12 with serum negative RA (1428 joints), increased accumulation of HIG, concerning serum positive patients, has been mentioned to 163 joints ("arthritic changes"), whilst in the same group, BS revealed degenerative changes to 265 joints. Concerning serum negative patients, the respective results were 64 versus 190 joints. Increased uptake of HIG has been found in 189/226 swollen and painful joints (overall sensitivity according to clinical criteria 83.3%) and in 38 joints without any clinical evidence of inflammation, with clinical active inflammation presented after follow-up to 35 of them, yielding thus specificity at the level of 92%.

Matched findings between these two methods have been mentioned to 185 out of 227 joints with an abnormal scan with HIG. Abnormal x-rays and US findings have been mentioned in 67 of the joints.

Conclusions: According to the above mentioned, BS in RA reveals joints being actively inflamed or not, whilst radionuclide study with HIG is capable to distinguish actively inflamed joints, even in patients with serum negative RA, in a greater extent than anatomical imaging modalities. Hippokratia 2011; 15 (1): 37-42

Key words: rheumatoid arthritis, bone scan, human polyclonal immunoglobulin (^{99m} Tc-HIG), radionuclide imaging.

Corresponding author: George Gerasimou, 2nd Laboratory of Nuclear Medicine, AHEPA University Hospital, 1, St Kyriakidi street 54636-Thessaloniki-Greece, Tel: +302310-993136, E-mail: george_gerasimou@yahoo.gr

Rheumatoid arthritis (RA) is a chronic disease with the characteristic feature of persistent inflammatory synovitis. Tendon and bursal involvement are frequent and clinically dominant in early disease[1]. The pathology involves two steps generally known as exudative and infiltrative phases. During the first phase there is an increased capillary permeability of the synovial membrane and exudation of plasma proteins into the synovial stroma and the joint cavity, whilst the second phase consists of infiltration of cellular elements[1,2].

The synovial inflammation causes cartilage destruction, bone erosions and joint deformities. Most of patients with RA and/or polyarthritic syndromes (PS) suffer from persistent and fluctuating disease activity and episodes of active inflammation and joints' deformity. This variability determines the therapeutic strategy of rheumatologists[3]. Methods include subjective score of joint pain and swelling. However, there is need for an objective method to assess disease activity in the involved joints as the "gold standard" which will be helpful in the management of patients suffering from RA.

Bone scan is a sensitive, however non-specific diagnostic tool to study bone diseases, whilst in patients with RA, the feature is increased uptake unrelated to disease activity. Increased uptake of the radiopharmaceutical could be attributed to remission with coexisting reactive bone repair[4]. Three-phase bone scanning is capable to show indications of active inflammation in selected joints, but it is impossible to perform a whole body dynamic acquisition in cases of polyarthritic syndromes.

Biopsy of joints of interest is a painful and not tolerated by the majority of patients method.

The lack of specificity of bone scan in the detection of active inflammation is leading to radionuclides with high affinity to the inflammatory process. Nonspecific polyclonal human immunoglobulin G (HIG), labeled with ^{111}In or ^{99m}Tc, has been introduced as a more specific agent for the detection of infection and inflammation with a high diagnostic accuracy[5-8]. ^{99m}Tc agent is preferred due to its lower radiation burden, better imaging quality due to the physical characteristics of ^{99m}Tc and lower cost of the procedure[9]. ^{99m}Tc radiolabeled human immunoglobulin IgG showed higher accumulation at the site of inflammation compared to ^{67}Ga-citrate, radiolabeled albumin and nanocolloid[10].

The attributes of technetium-99m labeled polyclonal IgG (^{99m}Tc-HIG-Technescan), has prompt us to clarify the suitability of the agent for imaging active synovial inflammation in patients with PS and RA, in comparison with bone scan and anatomic imaging modalities**.**

Materials and methods

From November 2006 to April 2008 a total of 40 patients (31 females), with a mean age of 45.3± 7 (range 34-55) and a disease duration of 15-24 months (range 18.3± 4.2) suffering from PS, were enrolled in the study. Twenty-six of the patients were serum positive to RA factor, considered as suffering from RA, whilst fourteen of them were RA factor negatives and they were considered suffering from serum-negative polyarthritic syndrome.

A detailed clinical examination has been performed to all patients, and laboratory biochemical tests indicated in cases of RA and PS were carried out, including:

White Blood Cells (WBC), Red Blood Cells (RBC), Hemoglobin (Hb), Hematocrit (Ht), Platelets (Plt), Erythrocyte Sentimentation Rate (ESR), Rheumatoid Factor (RF) test, Anti-citrullinic antibody (Anti-CCP), IgG, IgA and IgM immunoglobulins C-Reacting Protein (CRP), Anti-Nucleonic Antibodies (ANA), Histocompatibility Antigen B27 (HLAB27).

All patients were submitted to anatomical imaging modalities with x-rays and ultrasound of joints, plus radionuclide ones, including bone and HIG scanning.

Bone scanning was performed in a single-headed GENESYS γ-camera equipment (ADAC, Milpitas, Ca, USA) connected to a PEGASYS computer, 2-3 hours post iv injection of 740MBq of methyleno-diphosphonate labeled with ^{99m}Tc (^{99m}Tc-MDP-Mallincckrodt Medical B.V., Petten, The Netherlands). In 20 of the patients, dynamic acquisition (arterial and blood pool phase) was done in joints of interest accordingly to patients' complaints for pain. Five days apart from this, scanning with ^{99m}Tc labeled human immunoglobulin G (^{99m}Tc-HIG-Mallincckrodt Medical B.V., Petten, The Netherlands) was performed, 4 hours post iv injection of 555MBq of the radiopharmaceutical.

Forty-two joints were investigated with bone scan and ^{99m}Tc labeled human immunoglobulin G (^{99m}Tc-HIG) scintigraphy in each patient numbering: shoulders (2), elbows (2), wrists (2), metacarpophalangeal (10), proximal interphalangeal (10), distal interphalangeal (8), hips (2), knees (2), ankles (2) and sacro-iliac joints on the left and on the right side (2), numbering a total of 1680 joints. Anatomical imaging modalities have been performed only to joints of interest (joints with local pain and/ or edema).

Results

Accordingly to the HIG scanning results, patients were divided into two groups: Group A, including patients with a negative HIG scanning, considered as having inactive disease, and Group B, including the patients with positive HIG scanning, who were considered to have active disease.

In 6 of the patients-two with serum negative arthritis (252 joints), radionuclide imaging with HIG was within normal limits, despite the fact that in bone scan degenerative alterations have been mentioned in 30 of the joints. In all these patients disease was evaluated as inactive ("arthrotic changes").

In the remaining 34 patients-12 with serum negative arthritis (1428 joints), increased accumulation of HIG has been mentioned to 227 of the joints ("arthritic changes"), whilst BS revealed degenerative changes to 455 joints. Results are summarized in Table 1.

Concerning patients with active disease, two subgroups have been created: Subgroup 1 (S1), consisting of serum (+) patients (positive RF test) and Subgroup 2 (S2), with serum (-) patients (negative RF test). Results concerning BS and HIG scanning findings in the above mentioned subgroups, are summarized in Table 2.

Increased uptake of HIG has been found in 189/226 "clinically active joints", in terms of their being swollen and painful, yielding thus a sensitivity accordingly to clinical criteria of 83.3% and in 38 joints without any clinical evidence of inflammation (Figure 1). Follow-up of the latter patients revealed clinical active inflammation

Table 1: Results of Bone and HIG scans in all patients.

Patients	BS (+)	HIG (+)
Group A	6 pts (30 joints)	0
Group B	34 pts (455 joints)	34 patients (227 joints)*

*p<0.05

Table 2: Results of Bone and HIG scans in serum positive and serum negative patients.

Pts with active disease	Serum (+) S1	Serum (–) S2
BS	22 pts/265 joints	12pts/190 joints
HIG scanning	22 pts/163 joints*	12 pts/64 joints*

*p<0.05

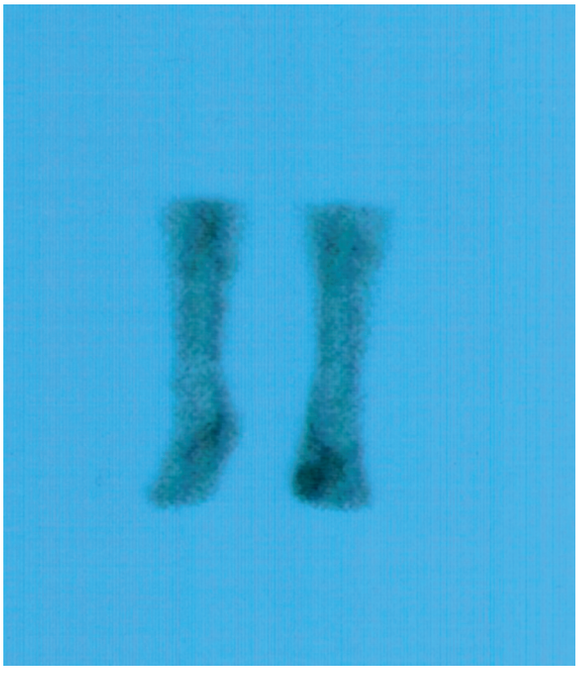

Figure 1: Female patient with painful ankle joints without signs of active inflammation: ^{99m}Tc-HIG scan revealed increased accumulation of the radioligand to both ankle joints compatible with active synovial inflammation. Increased local uptake of the radiopharmaceutical at the internal part of the soft tissues of the left foot is attributed to soft tissue inflammation.

to 35 of the above mentioned 38 joints, so specificity of the method accordingly to the clinical criteria of inflammation, was estimated as high as 92%.

Matched findings between HIG and BS have been found in 185/227 joints (81.5%) presenting active synovial inflammation. In Figure 2, concerning a male patient with polyarthritic syndrome with low back pain and negative bone scan HIG scan revealed increased accumulation of the radiopharmaceutical to the sacro-iliac joints, compatible with sacro-ilitis and enthesopathy.

Dynamic acquisition revealed increased arterial and blood pool phases, compatible with active inflammation to 18/40 studied joints of interest, whilst in the same joints BS showed increased accumulation of the radiopharmaceutical to 16 of them and HIG scanning in the same joints showed results matched to dynamic acquisition in the same 18, plus 2 more joints.

Anatomical imaging modalities (x-rays and US) have been performed in the 34 patients of Group B, in a total of 150 joints, with increased accumulation of the HIG, plus in 30 joints with no abnormal HIG findings, but abnormal BS findings, compatible with degenerative changes. Abnormal findings were found in 67 of the joints (53 joints with increased accumulation of HIG and 14 with abnormal BS findings). However, x-rays revealed only degenerative changes in the articular surfaces of the cartilage and bones and only US was capable to show indications of synovial inflammation in terms of villo-nodular synovitis, in 88/150 joints presenting active synovial inflammation in HIG scanning.

Discussion

The assessment of disease activity in patients with PS and/ or RA is a rather difficult procedure in terms of the lack of availability of a "gold standard". The number of swollen and painful joints is generally used to measure the degree of disease activity, but these variables are largely subjective and not reproducible[11]. The availability of an objective and reproducible method to evaluate disease activity in RA and PS would be of value. Joints' scintigraphy with polyclonal IgG immunoglobulin has the potential to provide an objective way to detect and quantify synovial inflammation in arthritis[5]. Labeling of IgG can be performed with ^{111}Indium[12,13] and ^{99m}Tc[5,14]. The advantages of ^{99m}Tc are its short half-life, suitable γ energy photons for acquisition, low cost, low radiation exposure and simple labeling procedure[9].

There are publications supporting the use of ^{99m}Tc-HIG in the evaluation of patients with RA and the differentiation between active and inactive disease. Berna et al have postulated increased uptake of ^{99m}Tc-DPD in both active and inactive joints in chronic RA, but increased ^{99m}Tc-HIG uptake is present only in actively inflamed joints[15]. In another study using an animal model it has been shown that ^{99m}Tc-IgG localizes in sites of collagen-induced arthritis and quantitative studies can be performed to assess the severity of the inflammation[10]. Other authors have correlated the degree of ^{99m}Tc-IgG uptake with clinical staging and/ or degrees of swelling[7,16]. According to our results the above mentioned agent is capable to distinguish active and non-actively inflamed joints and its uptake is correlated with clinical features, such as swelling and pain. The assessment of severity of

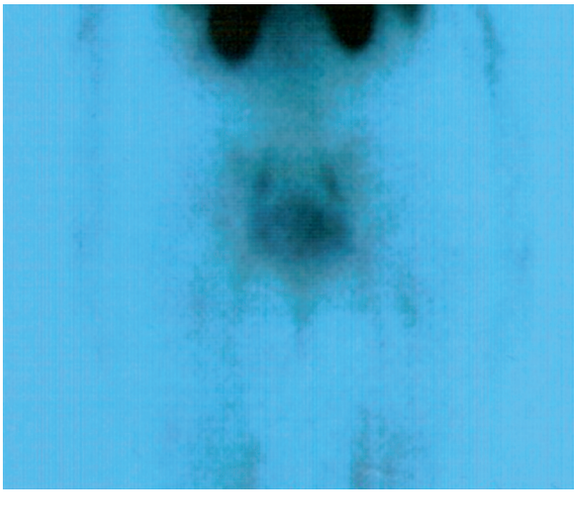

Figure 2: ^{99m}Tc-HIG scan in a male patient with low back pain and negative bone scan: increased accumulation of the radiopharmaceutical to the sacro-iliac joints, compatible with sacro-ilitis and enthesopathy.

inflammation, may not be feasible with this agent[15]. De Bois et al evaluated the sensitivity of ^{99m}Tc-IgG scintigraphy in testing for the detecting joints' swelling ranging between 78% for the ankles and 100% for the proximal interphalangeal joints[17]. Authors considered that swelling correlated more than pain with ^{99m}Tc-IgG scintigraphy, because in RA swelling is usually a manifestation of inflammation, whilst pain can be also produced by joint destruction. Our results are presenting an overall sensitivity of 83.3% and in addition we have mentioned increased uptake of the radiopharmaceutical in 38 joints without any clinical evidence of inflammation.

Since histological examination in order to prove active inflammation in these joints was not available, we can't be quite sure whether HIG scintigraphic results must be considered as false positive or whether this technique is superior to clinical examination with regard to the detection of arthritis. However, histologically proven inflammation of the synovial membrane, even in the absence of clinical signs of arthritis has been mentioned in cases of RA[18]. Similar results have been postulated by other authors who found that ^{99m}Tc-HIG scanning detected 87% of joints presenting signs of swelling and/ or pain[19]. In this publication significant correlations were found between individual scores of joint uptake and clinical scores of pain and swelling. In another study concerning the evaluation of patients with RA with ^{99m}Tc-HIG scintigraphy, pathological uptake of the radiopharmaceutical was noted in 46% of joints evaluated as painful, 89% of swollen joints and 94% of both painful and swollen joints[20]. Both the visual and the quantitative scintigraphic indices correlated significantly with the clinical index, the number of painful joints, the number of swollen joints and several biological markers of inflammation.

Of special interest are the results of de Bois et al who have mentioned that the sensitivity of ^{99m}Tc-IgG scintigraphy in detecting synovitis activity, as determined histologically (85%), was higher than the sensitivity of joint swelling (65%). In the absence of clinically detectable knee joint swelling the sensitivity of ^{99m}Tc-IgG scintigraphy was 83%[21]. Other authors reported that ^{99m}Tc-IgG scintigraphy had a sensitivity of 69% and specificity of 88% in cases with tenderness and 72% and 81%, respectively, in cases with swelling. Total scintigraphic scores were correlated with serum levels of C-reactive protein[22].

Liberatore et al[23] compared scintigraphic results between ^{99m}Tc-HIG scanning, scanning with ^{99m}Tc hexamethyl-propylenoamine-oxime (HMPAO) labeled white cells (^{99m}Tc-WBC) and with ^{99m}Tc-albumin nanocolloids (^{99m}Tc-NC) in cases of RA. According to these results ^{99m}Tc-HIG scanning seems to be more useful than ^{99m}Tc-NC in the initial stages of the disease, whilst ^{99m}Tc-WBC scanning was negative in a consistent percentage of the joints previously assessed as clinically and ^{99m}Tc-HIG scanning positive. The greater frequency of ^{99m}Tc-HIG scanning positivity at the beginning of the disease compared to ^{99m}Tc-NC is the different kinetic of the tracers to the inflammation sites. ^{99m}Tc-NC penetrates the synovium due to increased capillary permeability[24]. The uptake of ^{99m}Tc-HIG at the synovial membrane in cases of RA is influenced by the exudation of plasma proteins and the presence of immunoglobulin Fc-fragment receptors on the inflammatory cellular infiltrate[25,26]. The discrepancy of the results between ^{99m}Tc-HIG plus clinical examination and ^{99m}Tc-WBC scan is attributed to the indication that leucocytes reach a significant concentration in the inflamed joints after the clinical signs of the disease have appeared[21]. Other authors have supported that ^{99m}Tc-HIG scintigraphy can be used as a non-invasive objective parameter to monitor arthritis activity in patients with RA pre and post intra-articular corticosteroid treatment[27]. In another study, clinical and laboratory variables of arthritis activity as well as the scores of ^{99m}Tc-IgG scintigraphy were significantly lower after gold treatment compared to the scores before treatment. However, the difference between the mean scores of ^{99m}Tc-IgG scintigraphy before and after treatment was statistically significant for more joints than such difference in scores for joint pain and joint swelling[28]. Other authors compared ^{99m}Tc-HIG and three-phase ^{99m}Tc-MDP bone scintigraphy for evaluating the efficacy of Yttrium-90 silicate radionuclide synovectomy[29]. According to their results, ^{99m}Tc-HIG scintigraphy appears to be a valuable method that complements clinical assessment of the efficacy of Y-90 silicate therapy in rheumatoid knee synovitis, starting in the early post-treatment period. However, three-phase ^{99m}Tc-MDP bone scintigraphy may be valuable in the late postsynovectomy period.

In our study, in the subgroup of patients with serum negative PS, a total of 64 joints presented increased uptake of ^{99m}Tc-HIG, compatible with active synovial inflammation. Other authors have reported that Tc-99m polyclonal immunoglobulin-G has been shown to be a successful agent in the depiction of active inflammation in rheumatoid arthritis and its variants[30]. All clinically active joints in variants of RA patients accumulated ^{99m}Tc-HIG and showed increased ^{99m}Tc-MDP uptake. These joints had a very similar Tc^{99m}-HIG retention pattern to the RA joints. The detection rate of active joint inflammation with ^{99m}Tc-HIG was much higher than that with ^{99m}Tc-MDP. Warchol et al has postulated that immunoglobulin G and nanocolloid accumulate preferentially in inflammatory joints and therefore might be useful to differentiate between inflammatory and degenerative lesions in patients with small joints arthritis[31]. In another publication concerning brucellosis with arthritis, bone scanning did not detect soft tissue complications, but ^{99m}Tc-HIG scintigraphy was useful for the detection of both osteoarticular and soft tissue complications[32]. Other authors in a patient with lupus erythematosous and polyarticular joint complaints, did not find abnormal IgG uptake compatible with active synovial inflammation[33].

The side effects of anti-inflammatory drugs given to improve the symptoms and quality of life of patients with RA can be reduced by the use of specific immunotherapies. The introduction of biological therapies for the management of RA started a revolution in the therapeutic armamentarium with the development of several novel monoclonal antibodies (mAbs). Monoclonal antibodies specifically bind to their target, which could be adhesion molecules, activation markers, antigen or receptors to interfere with specific inflammation pathways at the molecular level. These new generation of mAbs can be radiolabelled, directly or indirectly, by a variety of radionuclides, depending upon the specific diagnostic application. For the evaluation of RA patients, several mAbs and their fragments, including anti-TNF-α, anti-CD20, anti-CD3 and anti-E-selectin antibody, have been radiolabelled mainly with ^{99m}Tc or ^{111}In. The clinical impact of scintigraphy with these radiolabelled antibodies in RA patients is that it holds two types of information: 1) it allows better staging of the disease and diagnosis of the state of the activity by early detection of inflamed joints and 2) it might provide the possibility to perform evidence-based biological treatment of RA with a view to assess whether an antibody will localize an inflamed joint, before using the same unlabelled antibody therapeutically. This is of clinical importance for the selection of patients to be treated[34,35].

Positron emission tomography (PET) with fluoro-deoxy-glucose (FDG) may be helpful for early evaluations of the extent of RA throughout the whole body. FDG-PET represents the inflammatory activity of joints in patients with RA accurately and sensitively and the visual FDG uptake may be useful for evaluating metabolic activity of synovitis and measure the disease activity in RA[36]. In addition, FDG-PET has been proven useful in the detection of secondary active synovitis in osteoarthritic joints and in the majority of clinically inflamed joints[37]. Others have mentioned that visual assessment of FDG uptake shows a significant correlation with clinical evaluation of disease activity in patients with RA undergoing anti-inflammatory treatment[38]. Other PET radiopharmaceuticals binding to peripheral benzodiazepine receptors expressed on macrophages, have been proven to be useful to quantify inflammation in patients with RA[39]. However, PET studies are much more expensive than HIG scanning and they are not widely used in order to evaluate patients suffering from RA and PS.

Conclusions

According to the above mentioned, BS in RA and PS reveals joints being actively inflamed or not, whilst radionuclide study with ^{99m}Tc-HIG is capable to distinguish actively inflamed joints, even in patients with serum negative PS. In addition radionuclide imaging with IgG human polyclonal immunoglobulin can detect active synovial inflammation prior to clinical signs and in a greater extent than anatomical imaging modalities.

References

1. Grassi W, de Angelis R, Lamanna G, Cervini C. The clinical features of rheumatoid arthritis. Eur J Radiol. 1998; 27, Suppl 1: S18-24.
2. Ziff M. General mechanisms of inflammation in rheumatoid arthritis. Bull Zweiss Akad Med Wiss. 1979; 35: 275-281.
3. van de Heijde DM, van't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuven MA et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis. 1990; 49: 916-920.
4. Rosenthall L, Lisbona R. Noninfectious arthritis and allied disorders. In: Rosenthall L. Skeletal Imaging ACC, Norwalk 1984; 85-109.
5. Buscombe JR, Lui D, Ensing G, de Jong R, Ell PJ. ^{99m}Tc-human immunoglobulin (HIG)-first results of a new agent for the localization of infection and inflammation. Eur J Nucl Med. 1990; 16: 649-655.
6. Goh AS, Aw SE, Sundram FX, Ang ES, Leong KH. Imaging of focal inflammation with ^{99m}Tc-labeled human polyclonal immunoglobulin G. Nucl Med Commun. 1990; 11: 843-856.
7. van der Lubbe PA, Amdt JW, Calame W, C, Pawels EK, Breedveld FC. Measurement of synovial inflammation in rheumatoid arthritis with technetium 99m labeled human polyclonal immunoglobulin G. Eur J Nucl Med. 1991; 18: 119-123.
8. Galli G, Salvatori M, Antoni M et al. ^{99m}Tc-human immunoglobulin (HIG) in AIDS patients: first results. J Nucl Biol Med.1991; 35: 14-20.
9. Saptogino A, Becker W, Wolf A. Biokinetics and estimation of dose from ^{99m}Tc-labelled polyclonal human immunoglobulin (HIG). Nuklearmedizin. 1991; 30:18-23.
10. Breedvekd FC, van Kroonenburgh MJPG, Camps JAJ, Feitsma HIJ, Markusse HM, Pawels EK. Imaging of inflammatory arthritis with ^{99m}Tc-labeled IgG. J Nucl Med. 1989; 30: 2017-2021.
11. Bull BS, Westengard JC, Furr M, Bacon PA, Meyer PJ, Stuart J. Efficacy of tests used to monitor rheumatoid arthritis. Lancet. 1989; 2: 965-967.
12. Fischman AJ, Rubin RH, Khaw BA, Callahan RJ, Wilkinson R, Keech F et al. Detection of acute inflammation with In-111-labeled non-specific polyclonal IgG. Semin Nucl Med. 1988; 18: 335-344.
13. Rubin RH, Fischman AJ, Callahan RJ, Khaw BA, Keech F, Ahmad M et al.. In-111-labeled non-specific immunoglobulin scanning in the detection of focal infection. N Engl J Med. 1989; 321: 935-940.
14. Blok D, van Ogtrop M, Arndt JW, Camps JA, Feitsma RI, Goedemans W et al.. Detection of inflammatory lesions with radiolabeled immunoglobulins. Eur J Nucl Med. 1990; 16: 303-305.
15. Bernα L, Torres G, Cesar D, Montserrat E, Martinez-Duncker D, Carrió I. Technetium-99m human polyclonal immunoglobulin G studies and conventional bone scans to detect active joint inflammation in chronic rheumatoid arthritis. Eur J Nucl Med. 1992; 19: 173-176.
16. Becker W, Horneff G, Saptogino A, Burmester G, Wolf F. ^{99m}Tc-labeled unspecific immunoglobulin in rheumatoid arthritis (abstract). J Nucl Med. 1991; 32: 983.
17. de Bois M, Arndt JW, van der Velde EA, van der Lubbe PA, Westedt M, Pawels EK et al. ^{99m}Tc Human Immunoglobulin Scintigraphy-A reliable method to detect joint activity in rheumatoid arthritis. J Rheumatol. 1992; 19: 1371-1376.
18. Soden M, Rooney M, Cullen A, Whelan A, Feighery C, Bresnihan B. Immunohistological features in the synovium obtained from clinically uninvolved knee joints of patients with rheumatoid arthritis. Br J Rheumatol. 1989; 28: 287-292.
19. Pons F, Moyα F, Herranz R, Sola M, Del Olmo JA, Piera C et al. Detection and quantitative analysis of joint activity inflammation with ^{99m}Tc –polyclonal human immunoglobulin G. Nucl Med Commun. 1993; 14: 225-231.

20. Pons F, Sanmarti R, Herranz R, Collado A, Piera C, Vidal-Sicart S et al.. Scintigraphic evaluation of the severity of inflammation of the joints with ^{99m}Tc-HIG in rheumatoid arthritis. Nucl Med Commun. 1996; 17: 523-528.
21. de Bois M, Tak PP, Arndt J, Kluin PM, Pawels EK, Breedveld FC. Joint scintigraphy for quantification of synovitis with ^{99m}Tc-labelled human immunoglobulin G compared to histological examination. Clin Exp Rheumatol. 1995; 13: 155-159.
22. Cindaş A, Gökçe-Kustal Y, Kirth PO, Caner B. Scintigraphic evaluation of synovial inflammation in rheumatoid arthritis with (99m)technetium-labelled human polyclonal immunoglobulin G. Rheumatol Int. 2001; 20: 71-77.
23. Liberatore M, Clemente M, Iurilli A, Zorzi M, Marini L, Di Rocco E et al.. Scintigraphic evaluation of disease activity in rheumatoid arthritis: a comparison of technetium-99m human non-specific immunoglobulins, leucocytes and albumins nanocolloids. Eur J Nucl Med. 1992; 19: 853-857.
24. De Schrijver M, Streule K, Senekowitsch R, Fridrich R. Scintigraphy of inflammation with nanometer-sized colloidal tracers. Nucl Med Commun. 1987; 8: 895-908.
25. Morrel EM, Tompkins A, Fischman AJ, Wilkinson RA, Burke JF, Rubin RH et al. Autoradiographic method for quantitation of radiolabeled proteins in tissues using indium-111. J Nucl Med. 1989; 30: 1538-1545.
26. Fischman AJ, Wilkinson R, Khaw BA, Callahan R J, Ahmad M,. Locke E, et al. Imaging of localized bacterial infections with radiolabeled non-specific antibody fragments (abstract). J Nucl Med. 1988b; 29 [Suppl]: 610.
27. de Bois M, Arndt J, Tak PP et al. ^{99m}Tc-labelled polyclonal human immunoglobulin G scintigraphy before and after intra-articular knee injection of traimcinolone hexacetonide in patients with rheumatoid arthritis. Nucl Med Commun. 1993; 14: 883-887.
28. de Bois M, Westedt M, Arndt J, Wiarda KS, van der Velde EA, Pauwels EK et al. Technetium-99m labelled polyclonal human IgG scintigraphy before and 26 weeks after initiation of parenteral gold treatment in patients with rheumatoid arthritis. J Rheumatol. 1995; 22: 1461-1465.
29. Arzu-Genoglu E, Aras G, Kucuk O, Atay G, Tutak I, Ataman S et al. Comparison of ^{99m}Tc-HIG and three-phase ^{99m}Tc-MDP bone scintigraphy for evaluating the efficacy of Yttrium-90 silicate radionuclide synovectomy. Clin Nucl Med. 2003; 28: 277-285.
30. Sahin M, Bernay I, Basoglu T, Canturk F. Comparison of ^{99m}Tc-MDP, ^{99m}Tc- HSA and ^{99m}Tc-HIG uptake in rheumatoid arthritis and its variants. Ann Nucl Med. 1999; 13: 389-395.
31. Warchol O, Kφnig B, Dworak E, Kφhn H, Dunky A, Mostbeck A. Value of inflammation and bone scintigraphy in differential diagnosis of painful affections of small joints. Acta Med Austriaca. 1998; 25: 7-12.
32. Kadanali A, Varoglu E, Kerek M, Tasyaran MA. ^{99m}Tc-polyclonal human immunoglobulin scintigraphy in brucellosis. Clin Microbiol Infect. 2005; 11: 480-485.
33. Jacobs F, Dierckx RA, Vranken E, De Vos F, Van de Wiele C. Absence of increased ^{99m}Tc-polyclonal human immunoglobulin (HIG) joint uptake in a patient with systemic lupus erythematosus presenting with polyarticular joint complaints. Clin Nucl Med. 2005; 30: 124-125.
34. Chianell M, D' Alessandria C, Conti F, Priori R, Valesini G, Annovazzi A, et al. New radiopharmaceuticals for imaging rheumatoid arthritis. Q J Nucl Med Mol Imaging. 2006; 50: 217-225.
35. Malviya G, Conti F, Chianelli F, Scopinaro F, Dierckx R.A, Signore A. Molecular imaging of rheumatoid arthritis by radiolabelled monoclonal antibodies: new imaging strategies to guide molecular therapies. Eur J Nucl Med Mol Imaging. 2010; 37: 386-398.
36. Beckers C, Ribbens C, Andrı B, Marcelis S, Kaye O, Mathy L et al. Assessment of disease activity in rheumatoid arthritis with (18) F-FDG PET. J Nucl Med. 2004; 45:956-964.
37. Elzinga EH, van der Laken CJ, Comans EF, Lammertsma AA, Dijkmans BA, Voskuyl AE. 2-Deoxy-2-[F-18] fluoro-D-glucose joint uptake on positron emission tomography images: rheumatoid arthritis versus osteoarthritis. Mol Imaging Biol. 2007; 9: 357-360.
38. Goerres GW, Forster A, Uebelhart D, Seifert B, Treyer V, Michel B et al. F-18 FDG whole-body PET for the assessment of disease activity in patients with rheumatoid arthritis. Clin Nucl Med. 2006; 31: 386-390.
39. Kropholler MA, Boellaard R, Elzinga EH, van der Laken CJ, Maruyama K, Kloet RW et al. Quantification of (R)-[11C]PK11195 binding in rheumatoid arthritis. Eur J Nucl Med Mol Imaging. 2009; 36: 624-631.