EVALUATION OF JOINT INFLAMMATION IN RHEUMATOID ARTHRITIS: A CORRELATIVE STUDY WITH Tc-99m HIG SCINTIGRAPHY AND CLINICAL FINDINGS

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SUMMARY

Purpose: *Concordance between clinical and Tc-99m HIG scintigraphy evaluations in patients with rheumatoid arthritis was evaluated.* ***Material & Method:*** *Forty patients fulfilling the ARA criteria were investigated. For scoring the pain and swelling in the joints, Ritchie articular index was used. Tc-99m HIG scintigraphic assessment was performed at 4 and 24 hours post injection. Simultaneously with scintigraphic evaluation, ESR and CRP levels were investigated. Kappa and Spearman correlation analysis was used for statistical analysis.* ***Results:*** *Sensitivity and specificity of Tc-99m HIG scintigraphy for painful joints were 59% and 54% respectively. As for swelling, sensitivity rate was 63%; specificity rate was 58%. These values were found to be higher in MCP, PIP and wrist joints in comparison with larger joints.* ***Conclusion:*** *Although Tc-99m HIG scintigraphy is suggested to be an objective agent for routine use in detecting active inflammation, it should be used in selected cases since the sensitivity and specificity values are not very high and the radiopharmaceutical is fairly expensive.*

Key Words: *Rheumatoid Arthritis, Inflammation, HIG Scintigraphy, Articular Index.*

INTRODUCTION

Tc-99m and In-111 labelled non-specific polyclonal human immunoglobulin (HIG) scintigraphy has been found reliable in the diagnosis of infection and inflammation (1-3). Some researches have shown that HIG between scintigraphy can be useful in differentiating degenerative changes and inflammation in joints (4-6). It has been claimed that the scintigraphic uptake is related to the degree of synovial inflammation. In several studies performed on patients with rheumatoid arthritis (RA) a correlation between visual scoring of the scintigraphic uptake and the clinical scores (pain, swelling) has been documented (6-8). In animal models of collagen induced arthritis, also a correlation was found between clinical joint scores and quantitative scintigraphic assessments (8).

In general, the number of painful and swollen joints measures the activity of inflammatory arthritis clinically. However, using clinical parameters may be subjective and not reliable (9,10). A number of laboratory markers of inflammation are used in order to assess disease activity more objectively; CRP, serum

amyloid A, haemoglobin, platelet counts and ESR are the most frequently used (11). More recently serum levels of IL-6, TNF-α, sIL-2R have been proposed to reflect clinical disease activity (12). However, at present there is still no gold standard for assessing arthritis activity precisely.

The purpose of this study was to evaluate whether Tc-99m HIG scintigraphy is useful in determining activity of synovial inflammation in RA and the concordance between clinical and scintigraphic evaluations.

MATERIAL AND METHODS

Forty patients fulfilling the ARA criteria for RA were investigated with HIG scintigraphy between September 1995- July 1996. Informed consent was obtained from each patient.

Clinical evaluation:

The clinical evaluation of patients was carried out by the same physiatrist. For the scoring of arthritis, Ritchie articular index was used and the presence or absence of pain and swelling was noted in each patient in nine joint areas: Shoulder, elbow, wrist, MCP, PIP, hip, knee, ankle and MTP. Nine joint groups (18 joints) were evaluated in 40 patients, a total of 720 joints. Pain and swelling was scored between 0-3. In addition, every joint was indexed according to the presence or absence of pain and swelling: (1=positive (for Ritchie scores 1,2,and 3), 0= negative (for Ritchie score =0)) (5).

Laboratory investigations:

ESR and CRP were investigated in all patients simultaneously with scintigraphic evaluation.

Scintigraphic evaluation:

1mg modified polyclonal human immunoglobulin G (Technescan HIG, Mallinckrodt Medical BIO, Petten, Holland) was bound by Tc-99m pertechnetate according to the instructions of the manufacturer. After iv injection of 740MBq, imaging was performed at 4-hour and 24-hour using a large field-of-view digital gamma camera, equipped with a low energy, high-resolution collimator. Anterior spot images of the joints were obtained at a pre-set time of 7 minutes with 256X256 quantitative matrix. Two experienced nuclear medicine physicians who were blind to the clinical data evaluated scintigraphic studies. All the joints were visually scored between 0-3, 0 being baseline activity, 1: mild increase, 2: moderate increase and 3: marked increase. Another index for scintigraphic evaluation was formed according to absence or presence of scintigraphic activity, 0= baseline activity, 1= increased activity. A consensus was reached between the two physicians in case of discordance when evaluating the scintigraphic views.

True positive, true negative, false positive and false negative ratios were calculated for pain and swelling based on the classification below:

True positive: Positive scintigraphic uptake with clinical pain and swelling. False positive: Positive scintigraphic uptake without clinical pain and swelling. True negative: Negative scintigraphic uptake without clinical pain and swelling. False negative: Negative scintigraphic uptake with clinical pain and swelling.

Based on this analysis, the sensitivity, specificity and accuracy, and positive and negative predictive values were obtained. The concordance of Tc-99m HIG scintigraphic uptake with parameters of laboratory and clinical disease activity was investigated (9).

Statistical analysis:

Clinical and scintigraphic scoring and indexes and ESR and CRP were evaluated separately with kappa analysis. Clinical and scintigraphic indices were correlated by Spearman correlation analysis.

RESULTS

Thirty-four patients were women (84%), 6 were men (6%) with a mean age of 50.5±14.6 years (15-76 years). Duration of illness was between 0.25- 40 years with a mean of 11.9±8.9 years. All patients were RF positive. The mean+SD values of ESR and CRP were 40.8±23.8 (3-110mm/h) and 36.4±35.9 (6-96mg/l) respectively. 52% of joints were positive at 4-hour HIG scintigraphy (375/720) while 53% were positive at 24-hour HIG scintigraphy (Fig. 1,2). Scintigraphic scores of the two observers

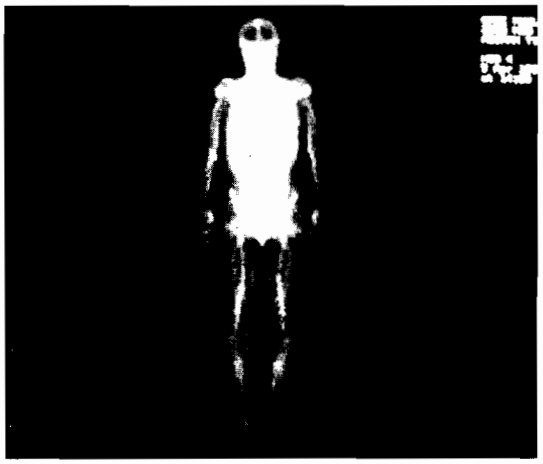

Fig. 1: Anterior whole body scintigraphy with Tc-99m HIG in a clinically non-active RA patient without synovitis of peripheral joints.

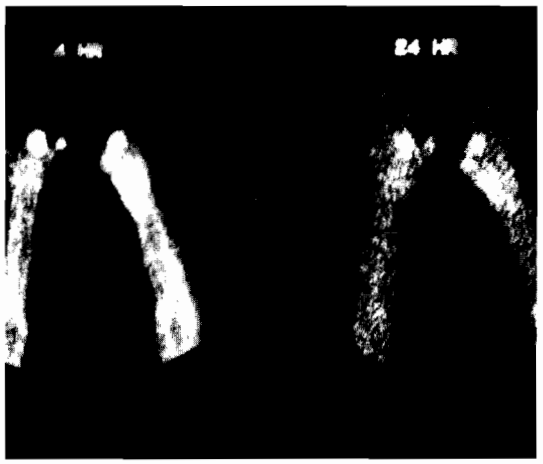

Fig. 3: Tc-99m HIG scintigraphy performed at 4h and 24h in a patient suffering from active synovitis. Pathological uptake is observed in the first and second metacarpopharengial joints in both hands.

were well correlated ($r=0.82$, $p<0.001$). Strong correlation was found between 4-hour and 24-hour HIG scintigraphic uptakes ($r=0.91$, $p<0.001$) (Fig. 3), thus only the results of 24-hour HIG scintigraphy are shown in tables. Pain and swelling were positive in 58 % (420/720) and 48% (351/720) of the joints respectively. The percentage of joints which had neither swelling nor pain was 32% (236/720). In 67% of joints (484/720) there was either pain or swelling. The percentage of positive joints for both pain and swelling was 39% (287/720).

Swelling compared with 24-hour HIG scintigraphic uptake:

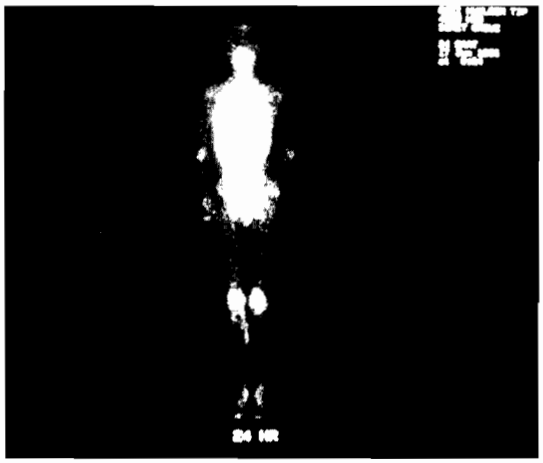

Fig. 2: Anterior whole body scintigraphy with Tc-99m HIG in a patient with RA with arthritis of the right and left elbows, wrists, fingers and knees.

True positive ratio at 24-hour HIG scintigraphy was 63% (224/351). True negative ratio was 56% (207/369). The percentage for false negative ratio (swelling with negative scintigraphic uptake) was 36% (127/351); while the percentage for false positive ratio (swelling with positive scintigraphic uptake) was 43% (162/369). The accuracy of 24 hour HIG scintigraphy was 59%, sensitivity 63%, specificity 56%, negative predictability 61%, positive predictability 58% (Table 1).

Pain compared with 24-hour HIG scintigraphic uptake:

True positive ratio was 59% (250/420). The percentage for true negative ratio (no pain, no scintigraphic uptake) was 54% (164/300). False negative ratio (pain with negative scintigraphic uptake) was 40% (170/420). False positive ratio (no pain with positive scintigraphic uptake) was 45% (136/300). The accuracy of Tc^{99m} HIG in detecting painful joints was 57%, its sensitivity and negative predictability were 49 % and 64% respectively while its specificity was 54% (table 1).

Pain and swelling compared with 24-hour HIG scintigraphy:

In patients who had both swelling and pain in their joints, scintigraphy was positive in 66%, (191/287). In patients who had either pain or swelling, 24 hour HIG scintigraphy was positive in 58% (283/484). In patients who had either pain or swelling scintigraphy was negative in 56% (133/236).

When the clinical pain and swelling

Table 1: Overall percentages of specificity, sensitivity, true positive rate, positive and negative predictability of pain, swelling and the clinical indices.

	Sensitivity	Specificity	True (+)	(+) Predictability	(-) Predictability
Pain	59%	54%	57%	64%	49%
Swelling	63%	56%	59%	58%	61%

Table 2: Sensitivity and specificity ratios in different joint groups at 24-hour HIG scintigraphy.

24-hour scintigraphy (%)				
	Pain		Swelling	
JOINTS	Sensitivity	Specificity	Sensitivity	Specificity
Shoulder	59	50	50	55
Elbow	46	51	61	59
Wrist	78	18	82	31
MCP	70	60	70	52
PIP	46	81	50	79
Hip	-	84	-	87
Knee	65	60	50	30
Ankle	61	21	62	33
MTP	69	23	76	29

Table 3: Correlation coefficients between scintigraphy and clinical scores in different joints.

	Elbow	Wrist	MCP	PIP	Knee
Pain	*	0.17	0.31	0.19	0.19
Swelling	0.23	*	0.26	0.31	*

Kappa (r) $p<0.05$
* : no correlation was found

Table 4: Correlation coefficients between pain, swelling, ESR, and CRP in the whole joints.

	R	P
Total pain index	0.39	0.001
Total swelling index	0.44	0.001
ESR	0.63	0.001
CRP	0.40	0.001

scores were compared with HIG scintigraphy scores and indexes: 24-hour HIG scintigraphy in painful joints: Sensitivity varied from 46% (PIP joint), to 78% (wrist joint) and specificity varied from 60% (MCP joint) to 84% (hip joint). 24-hour HIG scintigraphy in swollen joints: Sensitivity varied from 50% (knee, PIP, shoulder joints) to 82% (wrist joint) and specificity varied from 52% (MCP joint) to 87% (hip joint), (Table 2).

A correlation between clinical and scintigraphic indices was found. In joints most affected by RA, the strongest correlation was found between swelling and PIP joint at 24-hour HIG scintigraphy ($k=0.31$, $p<0.001$). The weakest correlation was found with pain in the wrist at 24-hour HIG scintigraphy ($k=0.17$, $p<0.05$) (Table 3).

When ESR, CRP, pain and swelling in the joints were compared separately, the correlation between ESR and pain and swelling was 0.28 and 0.36 respectively. The same correlation for CRP was 0.26 and 0.18. The correlation between HIG scintigraphy and ESR was 0.63; and 0.40 for CRP (Table 4).

DISCUSSION

It is important to detect early synovial inflammation in patients with RA. In order to prevent the sequelae of the disease, synovial inflammation, which leads to joint destruction, must be diagnosed as early as possible. Currently the activity of arthritis is followed up by subjective and non-specific clinical and laboratory parameters. Therefore studies on objective validation of disease activity and research are still continuing. Since the 1950's, radiopharmaceuticals are used for this purpose and different types have been developed. The advantage of imaging with radiopharmaceuticals is that the whole body and joints, including the ones difficult to evaluate with other radiological techniques and physical examination, can be viewed.

The mechanism of HIG accumulation in sites of inflammation is not clear. Researchers who have worked with In-111 have postulated that the effect is through the Fc receptors on the circulating monocytes (4,5) and hypothesised that binding to the Fc receptor carries the IgG to the inflammation site. However assignment of a major role of Fc part of the molecule and Fc receptor binding was rejected in later publications (13,14). Another probable mechanism is the increase in vascular permeability. De Bois et al. have postulated the binding to extracellular matrix proteins whose production is increased at the inflammation site. However this binding is not specific to RA (15,16).

In many studies, In-111 and Tc-99m HIG scintigraphy have been shown to be sensitive and specific in detecting inflammation and a strong correlation was found between clinical scores and joint involvement in various studies (7,17,18). In collagen induced arthritis, a correlation was found between quantitative scores and joint inflammation scores (7). Berna et al. have compared Tc-99m HIG and Tc-99m MDP bone scintigraphy and concluded that Tc-99m HIG scintigraphy was useful in distinguishing active and non-active inflammation, but not useful in detecting the degree of inflammation (4). The advantage of labelled IgG scintigraphy is that it is a very well known radiopharmaceutical and one of the most studied agents in detecting active inflammation. Other advantages are that it remains stable in the circulation, binds to Tc-99m, is easily available and radiation exposure is low.

The authors have found global sensitivity and specificity of 4-hour /24-hour HIG scintigraphy ratios as 58%/59% and 54%/54% respectively. For joint swelling these ratios were 62%/63% for sensitivity and 58%/58% for specificity. According to de Bois et al. correlation for swelling has been found to be higher; sensitivity varied between 78% (at the ankle joint), and 100% (PIP, wrist joints). Specificity varied from 13% (MCP joint) to 63% (ankle joint) (5). The higher ratios reported in these reports can be attributed to the fact that false negative and false positive ratios were assessed together and the studies were performed in a selected group of patients whose disease activity were probably more uniform. In the present study, patients were randomly allocated. Without distinguishing the false positive ratio, Pons et al. have detected 87% of painful joints. If we had used the same method, the detection of painful joints in our study would have been 89%.

Assessment of swelling in the shoulder, hip and joints is difficult to evaluate and actual swelling is rarely observed (19). In addition, low correlation is observed between clinical and scintigraphic scores. In a study reported by Pons et al., swelling in the hip and especially at the ankle joint could not be evaluated (20). In our study, we have found a weak correlation between clinical parameters and Tc-99m HIG scintigraphy. However, a stronger correlation has been found between clinical and laboratory scores in small joints by de Bois et al (5). This finding is clinically very important as MCP, PIP and wrist are the joints most involved in RA.

Our false positive ratio (no swelling or pain with positive scintigraphy) in this study was 41%. Pons et al have reported this ratio to be 35% (20). It is difficult to interpret this ration as "false positive" because synovitis may not be ruled out in asymptomatic patients. High values of false positive ratios stated in literature as well as in our study highlight the fact that clinical parameters may not be adequate to distinguish subclinical inflammation. In a study reported by Soden et al, in the absence of clinical findings of arthritis, [synovial membrane inflammation was confirmed histopathologically] (21). In our study false positive ratios for pain at 4-hour and 24-hour HIG scintigraphy were 43% and 45% respectively.

In the literature this ratio has been reported as 10% (17). This discordance may be due to the presence of osteoarthritic changes with no real active inflammation and their effect on the clinical evaluation. In the same way, due to the osteoarthritic changes and deformities, swelling at the joints can be difficult to differentiate. Like many other studies, this study lacks a gold standard such as histopathological assessment.

The correlation between quantitative and visual scintigraphic scores has been reported in the literature (11,17). For this reason a careful visual evaluation is thought to be adequate for routine procedures (8). Quantitative analysis is time consuming but it may be useful in evaluating therapy response (6).

In our study a high correlation was found between 4 and 24-hour HIG scintigraphy ($r=0.91$, $p<0.001$). The true positive ratio was found to be higher at 24-hour HIG scans. As Tc-99m HIG is a blood pool agent, the decrease in background activity may lead to this effect. AlthoughTc-99m HIG is shown to be an objective agent for routine use in detecting active inflammation, we do not think that it is the gold standard for detecting synovitis considering the fact that the sensitivity and specificity values in our study are not as high as they are in other studies. It is also expensive for routine use.

However, in a selected group of patients, Tc-99m scintigraphy may be of great help in evaluating the degree of inflammation. Further studies evaluating the difference between pre and post therapy will be useful.

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