Measurement of joint inflammation in rheumatoid arthritis with indium-111 chloride

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Abstract

Studies in the collagen and rabbit models of arthritis have indicated that indium-111 chloride ($^{111}\text{InCl}_3$) scintigraphy objectively measures synovial inflammation. Indium-111 chloride scans, with imaging three days after 19 MBq intravenous injection, were performed on 21 patients with definite or classical rheumatoid arthritis (RA), all of whom were functional class II. Standard clinical indices of disease activity were recorded at the time of imaging by the same investigator, who was unaware of the results of joint scans. In addition, eight patients with severe osteoarthritis, four of whom were considered to need hip or knee joint replacement, were similarly scanned. In each patient 16 joints were graded as 0 to 5, based on increasing degrees of $^{111}\text{InCl}_3$ uptake, by a single investigator blinded to the patient's diagnosis and clinical status. In the group with RA significant correlations were observed between individual joint uptake on scan and peripheral joints with swelling, joints reported to be painful, and joints with any abnormality on physical examination. In the group with osteoarthritis joints positive on scan correlated with the presence of pain. A total scan score (sum of individual joint scores) was calculated for each patient. In the patients with RA values ranged from 0 to 42 with a mean (SEM) of 20.7 (2.7) and correlated with the number of swollen joints and decreasing grip strength. In the group with osteoarthritis the mean total scan score (9.2 (1.5), range 3-14) was significantly lower than in the patients with RA. These data show that $^{111}\text{InCl}_3$ scanning can measure joint involvement by RA.

Objective and non-invasive measurement of synovitis would be invaluable in assessing disease activity of patients with rheumatoid arthritis (RA). Traditional methods of grading synovitis, such as the number of swollen or painful joints, are subjective and may not reflect changes in this disease. Currently available scintigraphic techniques, such as technetium-99m pertechnetate, have been advocated for this purpose¹⁻⁵ but have received criticism owing to difficulties with interpretation and non-specificity.⁶

Other radiopharmaceuticals have been sought which might selectively identify inflamed synovium. The radiocations, gallium-67 (^{67}Ga)^{7,8} and indium-111 (^{111}In)^{9,10} have been proposed because they possess a high affinity for iron binding proteins.¹¹⁻¹⁵ Synovial iron is increased in RA,¹⁶⁻²⁰ and a close correlation

between the inflammatory infiltrate and synovial ferritin content has been described.^{16,20}

Gallium-67 has been investigated as a joint imaging agent in RA⁸ and shown, in a rabbit model of arthritis, to accumulate preferentially in the inflamed synovial tissue.⁷ Like ^{67}Ga citrate, $^{111}\text{InCl}_3$ has favourable gamma emissions and a short half life of 2.8 days.¹¹ Indium-111 chloride readily identifies cells expressing transferrin receptors,¹³⁻¹⁵ which are uniform markers of cell division,^{21,22} and competes more specifically than gallium for the iron binding site of transferrin.¹² Previous studies showed that $^{111}\text{InCl}_3$ radioimaging accurately defined the arthritic response of rats to immunisation with collagen.⁹ A comparison with technetium-99m dicarboxypropane-diphosphonic acid joint scanning in two patients with RA suggested that the $^{111}\text{InCl}_3$ joint scan more closely reflected their clinical status.⁹ Similar attributes were found for $^{111}\text{InCl}_3$ imaging in a rabbit model of antigen induced arthritis, where the histological severity of synovitis correlated closely with uptake.¹⁰ This study was conducted to evaluate further $^{111}\text{InCl}_3$ joint scintigraphy in patients with arthritis.

Patients and methods

PATIENTS

Twenty one outpatients fulfilling the American Rheumatism Association criteria for definite or classical RA²³ and eight patients with clinical and radiographic features of severe osteoarthritis of the hips and knees were recruited from the rheumatology clinic at our institution. The patients with RA were concurrently receiving non-steroidal anti-inflammatory drugs (19 patients), oral methotrexate 7.5 to 15 mg weekly (nine patients), prednisone 10 mg or less daily (eight patients), and parenteral gold (three patients). The patients with osteoarthritis were receiving non-steroidal anti-inflammatory drug treatment and had not received intra-articular injections. No patients were receiving iron treatment.

EVALUATIONS

Informed consent was obtained from patients and then $^{111}\text{InCl}_3$ joint scintigraphy was carried out as previously described.⁹ Each patient received 19 MBq $^{111}\text{InCl}_3$ intravenously, which exposes the patient to 2.5 mGy of whole body radiation (equivalent to the radiation exposure of 10 chest roentgenographs). Sixteen joint regions (hands, wrists, elbows, shoulders, hips, knees, ankles, and feet) were imaged at three

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days for five minutes in the late morning with an Anger scintillation camera interfaced to a computer. All views were anterior projections. Total scanning time was 30 to 45 minutes with total counts in joint regions of interest of 1000 to 5000. Ten per cent windows were set to detect the 173 and 247 keV peaks of ^{111}In . Data were stored in a 128×128 matrix. The stored computer images were analysed independently by two observers (JAP and WDJ), who were unaware of the patients' diagnosis or clinical status. A value of 0 to 5 was assigned to each joint, depending on the degree of uptake, as follows: 0=negative; 1=probably negative; 2=probably positive; 3=positive, faint; 4=positive; 5=positive, marked. By summing each patient's 16 joint scores, a total scan score was calculated. A computerised score was obtained from a ratio of the activity over the joint to that over an adjacent soft tissue region, after correction for background outside the patient.⁹

At the time of imaging a full examination was made of all the patients with RA by one investigator (RHS). Clinical data were recorded without knowledge of scan results. The methods used were those developed by the cooperating clinics committee of the American Rheumatism Association²⁴ and used in other studies.²⁵⁻²⁸ Grip strength was measured with the same folded sphygmomanometer after the cuff had been inflated to 20 mmHg. The degree of overall synovitis was graded as 0, 1, 2, or 3, according to a previously formulated scale.²⁹ The time required to walk 15 m, the duration of morning stiffness, and the number of anti-inflammatory and analgesic tablets or capsules ingested daily were recorded. The patient's global assessment of status was graded.²⁵ For the patients with osteoarthritis the investigator conducted a chart review and an examination for diarthrodial joints with pain, swelling, or deformity. In both patient groups a joint was considered to be abnormal on examination if swelling, deformity, pain on palpation or passive motion, or a restricted range of motion was detected.

STATISTICAL ANALYSIS

Correlations between positive (score ≥ 2) or negative (score ≤ 1) scans and swelling, pain, or any abnormality on examination were calculated with the χ^2 test of association. Correlations between total scan score and clinical disease variables were calculated with the Pearson product-moment correlation coefficient. Comparison between the mean total scan score of patients with RA and osteoarthritis was made with Student's two tailed t test. A p value of <0.05 was accepted as evidence of significance.

Results

All 21 patients with RA were judged to be functional class II.³⁰ Table 1 presents the other clinical characteristics of these patients and of the eight patients with osteoarthritis. Four of the eight patients with osteoarthritis had been advised to have hip or knee replacement, but

Table 1: Demographic and clinical characteristics of the 21 patients with rheumatoid arthritis and the eight with osteoarthritis undergoing $^{111}\text{InCl}_3$ joint scanning

Rheumatoid arthritis	
Average age (range)	52 (35-70)
Number female	16
Average years of disease duration (range)	8.1 (0.5-17)
Average number of painful joints (range)	6 (1-10)
Average number of swollen joints (range)	4 (0-10)
Average time (s) to walk 15 m (range)	11.2 (8.5-15.2)
Average grip strength (mmHg) (range)	93 (33-190)
Osteoarthritis	
Average age (range)	67 (48-76)
Number female	6
Average number of painful joints (range)	4 (2-6)

none had undergone surgery. Figures 1-3 show examples of $^{111}\text{InCl}_3$ scans.

A total of 444 joint regions from the patients with RA and osteoarthritis was considered by both observers to be visualised sufficiently well on scan to allow scoring. In 183 (41%) there was exact agreement in score. Disagreements by one to five grades occurred in 131 (30%), 70 (16%), 39 (9%), 20 (5%), and 1 (0.2%) joints respectively. Thus there was agreement within one score grade in 314 (71%) joints, and the two observers' scores were highly correlated ($\chi^2=158$, $p<0.0001$). Scoring of the ankles and feet differed markedly between observers, however. One observer had an average score of 1.38 for the ankles and feet, while the other had an average score of 3.00. Fourteen of the 21 disagreements by four or five score units occurred in the ankles or feet.

Figure 1: Anterior images of the shoulders, hands, hips, knees, and feet, obtained three days after intravenous injection of $^{111}\text{InCl}_3$, in a patient with rheumatoid arthritis. There is symmetrical, markedly positive uptake in the wrists and forefeet. Note the activity in the liver and bone marrow. In this patient the shoulders, wrists, and feet were painful and swelling was present in the wrists and proximal interphalangeal joints.

Figure 2: Anterior images of the shoulders, hands, hips, knees, and feet, obtained three days after intravenous injection of $^{111}\text{InCl}_3$, in a patient with osteoarthritis. There is only faint activity over the joints. A radioactive marker has been placed alongside the right hand and foot. In this patient the right wrist, left knee, and left shoulder were painful, but no joints were swollen.

Figure 3: Anterior images of the shoulders, hands, hips, knees, and feet, obtained three days after intravenous injection of $^{111}\text{InCl}_3$, in a patient with rheumatoid arthritis. There is markedly positive uptake in the left knee, positive uptake in the right wrist, hand, foot, and left ankle, and faintly positive uptake in the left wrist, hand, and foot. A radioactive marker has been placed alongside the right hand. In this patient the right shoulder, both elbows, wrists, hands, knees, ankles, and feet were painful and swelling was present in both wrists, hands, and the left knee and ankle.

The computerised score was difficult to implement owing to the varying background adjacent to the joint. An attempt was made to pick a representative region, but the computer calculations were heavily dependent on region selection. There was almost no correlation between the computer score and the subjective scan score, apparently because of background uptake. Subjective scan results depicted in the remainder of this paper, therefore, represent the readings of the senior radiologist (JAP).

STUDIES IN RA

Table 2 compares clinical findings and $^{111}\text{InCl}_3$ scans in the patients with RA. Of 248 individual joints, excluding the shoulders and hips, 77 were considered to be swollen. Forty four (57%) of the swollen joints were positive on $^{111}\text{InCl}_3$ scan. Of the 171 peripheral joints without swelling, 47 (27%) were positive. The overall agreement (positive scan with swelling present and negative scan with swelling absent) was 68%. The correlation between joint swelling and scan results was significant ($\chi^2=18.8$, $p<0.0001$). Similarly, a highly significant ($\chi^2=20.9$, $p<0.0001$) correlation was observed between individual joints reported to be painful and considered positive on scan. This assessment included the shoulders and hips. The overall agreement between painful joints and scan results was 65%. Indium-111 chloride joint scanning also correlated with joints that were both swollen and described as painful ($\chi^2=35.5$, $p<0.0001$) and with joints that showed abnormalities on physical examination ($\chi^2=6.1$, $p<0.02$). The overall agreement was 73% for swollen, painful joints and 55% for abnormal

Table 2: Clinical and $^{111}\text{InCl}_3$ radioimaging assessments in 21 patients with rheumatoid arthritis*

Clinical variable		Joints positive on $^{111}\text{InCl}_3$ scan No (%)	p Value
Swelling			
Present	(n=77)	44 (57)	
Absent	(n=171)	47 (27)	<0.0001
Pain			
Present	(n=134)	69 (51)	
Absent	(n=198)	52 (26)	<0.0001
Swelling and pain			
Present	(n=50)	37 (74)	
Absent	(n=198)	54 (27)	<0.0001
Examination			
Abnormal	(n=153)	68 (44)	
Normal	(n=179)	55 (31)	<0.02

*A total of 252 peripheral joints (excluding the shoulders and hips) were examined for swelling and 336 joints for pain and any abnormality. The number of joints on which comparisons are depicted (248 and 332 respectively) reflect the absence of a few joints from the imaged field.

Table 3: Number (%) of joints considered positive on $^{111}\text{InCl}_3$ scan in 21 patients with rheumatoid arthritis*

Joint	$^{111}\text{InCl}_3$ scan Number positive/total (%)
Hands	14/42 (33)
Wrists	23/42 (55)
Elbows	2/38 (5)
Shoulders	21/42 (50)
Hips	8/42 (19)
Knees	17/42 (40)
Ankles	21/42 (50)
Feet	19/42 (45)

*As described in table 2, analysis was performed on a total of 332 joints.

joints. Table 3 shows the number of positive scans in the various joints. There was no significant association between the computerised scores and any of the clinical variables.

The χ^2 test of association was also used to examine relations between clinical variables. After exclusion of pain in hips and shoulders joint pain was compared with swelling. Although these clinical variables were associated with one another ($\chi^2=11.2$, $p<0.001$), only 50 of 105 (48%) painful joints were also swollen. The overall clinical agreement between pain and swelling was 66%.

STUDIES IN OSTEOARTHRITIS

Among the eight patients with osteoarthritis, nine (30%) of the 30 joints reported as painful were positive on joint scan; of the 98 asymptomatic joints, nine (9%) were positive. The overall agreement was 77%. There was a significant ($\chi^2=8.2$, $p<0.01$) correlation between joints positive on scan and the presence of pain. Positive scans were not significantly associated with abnormalities on joint examination or the presence of swelling, which was rare. Joints positive on scan consisted of eight wrists, four knees, two hands, two hips, and two shoulders. It was not possible to distinguish between carpometacarpal and radiocarpal uptake in the positive wrists.

TOTAL SCAN SCORE

The mean (SEM) total scan score in the patients with RA was 20.7 (2.7) (range 0–42), while the mean score in the patients with osteoarthritis was 9.2 (1.5) (range 3–14). The difference between these means was significant ($p<0.001$). In the group with RA the total scan score correlated with the number of swollen joints (fig 4) and was inversely related to grip strength (fig 5). In neither group was there a significant association between the total scan score and other clinical or demographic variables measured.

Figure 4: Regression analysis ($r=0.562$, $p<0.01$) of the total scan score and the number of peripheral joints with swelling in the individual patients with rheumatoid arthritis.

Figure 5: Regression analysis ($r=-0.373$, $p<0.02$) of the total scan score and bilateral grip strengths in the individual patients with rheumatoid arthritis.

Discussion

In this study joint uptake of intravenously administered $^{111}\text{InCl}_3$ correlated significantly with conventional clinical measures of arthritis in a group of patients with RA who had varying duration of disease, pattern of joint involvement, and type of treatment. These findings support the suggestion that transferrin receptors are abundant in inflamed synovium³¹ and may indicate an important role for iron in the pathogenesis or perpetuation of the chronic synovitis seen in RA.^{16–20} The ability of $^{111}\text{InCl}_3$ to identify clinically active joints of patients with RA may make it a useful technique to detect, quantify, and monitor synovitis in this disease, and possibly in other conditions of chronic joint inflammation.

The sensitivity and specificity of diagnostic scanning with $^{111}\text{InCl}_3$ are difficult to calculate from this study. As there is no standard by which the cause of symptoms or signs of joint inflammation may be determined, even in patients meeting criteria for RA, we cannot rule out subclinical rheumatoid synovitis in a joint that is asymptomatic but positive on joint scan. Similarly, joints that were symptomatic or swollen but negative on $^{111}\text{InCl}_3$ scan may represent poor sensitivity, or may indicate that a process other than rheumatoid synovitis explains the clinical findings. The presence of pain and swelling correlated imperfectly with one another, again making it difficult to estimate the accuracy of $^{111}\text{InCl}_3$ joint scanning.

Patients with osteoarthritis generally had negative $^{111}\text{InCl}_3$ joint scans. The positive joint scans in these patients may represent subclinical inflammation ('inflammatory osteoarthritis') or may, alternatively, represent false positive results.

There was total disagreement (disagreement by four or five categories) between observers in 5% of readings. More than half of this disagreement was found to be due to a marked difference in interpretations of readings for ankles and feet. Caution also had to be used in interpreting shoulder and hip scans owing to the

occasional presence of contiguous bone marrow uptake. New criteria have been developed for this group of patients, which will be evaluated in further studies in an attempt to improve the precision of interpretation.

Scintigraphic experience with intravenously administered $^{111}\text{InCl}_3$ in patients with osteomyelitis has shown that this technique accurately detects infection.^{32, 33} Interestingly, positive scans without infection were encountered in two patients with inflammatory arthritis.³²

Although this study is the first systematically to relate clinical features of RA and osteoarthritis to $^{111}\text{InCl}_3$ scan results, it possesses the limitations commonly associated with scintigraphy.³⁴ As synovial fluid or biopsy material was not obtained from the joints of these patients we cannot be certain that uptake indicated inflammation. We have not repeated scans on individual patients to analyse whether changes in joint scans correlate with alterations in clinical status or treatment, nor have we followed up patients for long enough to know whether joints considered false positive on scan will eventually develop clinical disease.

The clinical evaluation of disease activity in RA is hampered by a lack of objective measures. Although the technique is sufficiently safe and the results in this study are promising, they must be considered preliminary. Further analysis will be required to determine the true value of $^{111}\text{InCl}_3$ joint scanning in individual patients with RA.

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