^{99m}Tc-albumin nanocolloid joint scintigraphy in rheumatoid arthritis patients who are in clinical remission – is remission real?

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Abstract

Objective

To make a comparison between the clinical data and the imaging results with ^{99m}Tc-nanocolloid scintigraphy in rheumatoid arthritis (RA) patients considered to be in remission.

Methods

Forty RA patients found to be in clinical remission according to the ACR and the EULAR (DAS28<2.6) criteria were studied. The group included 29 females and 11 males with a mean age of 60.8±13.5 years (range 22–86) and a mean disease duration of 13.4±7.7 years (range 2–23). The mean time of remission in the study group was 22.2±5.2 months (range 11-36). Each patient was given an intravenous injection of 555MBq of ^{99m}Tc-nanocalloid (NC). Spot views of the skeleton were taken and a SPECT-CT was done on the wrists and hands. A scan was considered positive when at least one of the hand joints showed increased tracer uptake.

Results

The ^{99m}Tc-nanocalloid scintigraphy was negative in 14 (35%) and positive for active joint disease in 26 (65%) patients. Twenty four out of the 26 patients with positive scan (92%) were sero-positive while those who had a negative scintigraphy were all sero-negative except one. No correlation was found between the type of treatment used, the time that elapsed from remission, or laboratory parameters (ESR CRP) and the scintigraphic results.

Conclusion

The clinical criteria used for remission in RA are not consistent with the actual inflammatory activity in the joints. These results are especially emphasised in the subgroup of sero-positive patients.

Key words

Rheumatoid arthritis, remission, joint scintigraphy, ^{99m}Tc-nanocolloid, inflammation, sero-positive

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Received on September 26, 2009; accepted in revised form on January 8, 2010.

Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is a chronic disease that affects almost 1% of the population and causes pain, radiological damage functional disability and reduced life expectancy (1).

The aim of treatment in RA is directed at suppressing the inflammatory process and establishing a state of remission. The new therapeutic modalities, especially the biologic agents introduced lately, have improved significantly the symptoms, radiologic outcomes and functioning of our RA patients. These new modalities, as well as the traditional DMARDs resulted in achieving clinical remission in 30-50% of patients in various clinical settings (2, 3). However, the definition of remission in RA remains controversial. The preliminary criteria for remission proposed by Pinals *et al*. in 1981 (4) that were adopted by the American College of Rheumatology (ACR) include six signs and symptoms of which at least five must be fulfilled for at least two consecutive months. Another index developed to measure disease activity in RA patients uses clinical as well as laboratory parameters (DAS score). Its modified version, which includes 28-joint count (DAS28), is widely used in Europe as a tool to measure disease activity, as well as a state of remission (4). Although the cut off point of DAS28 is still a matter of controversy, most authors and clinical studies use a value of less than 2.6 to define remission in RA (5, 6).

Recent studies have shown that there is a discrepancy between the clinical and laboratory parameters that indicate a state of remission and between various imaging techniques that assess synovial inflammation (7). Furthermore, a study carried out on 107 RA patients, who were judged by their rheumatologist to be in remission, revealed that 96% had synovitis on MRI, 73% had synovial hypertrophy on grey-scale US examination and 43% had increased power Doppler signal (8).

Conventional joint scintigraphy done with ^{99m}Tc-methylene diphosphonate yielded controversial results concerning its ability to detect active joint inflammation (9, 10).

The introduction of ^{99m}Tc-albumin nanocolloid (NC) scintigraphy some 20 years ago has proved to be an effective method for identifying patients with active peripheral joint disease (11, 12). Furthermore, this method was found to be highly correlated with dynamic and static MRI in patients with early RA (13) and has a sensitivity of 90% and a specificity of almost 100% in detecting inflammation (14). The proposed mechanism that stands behind the idea of using nanocolloid particles lies in the fact that small particulate substances were found to leave the circulation and enter the extravascular space at sites of inflammation due to local damage of the vascular endothelium and basement membrane. This theory is further strengthened by the fact that similar results of biodistribution have been achieved by using ^{67}Ga-citrate or ^{111} In-leucocyte scintigraphy (12).

Scientific evaluation of disease activity in RA can also be detected by the use of antibodies against granulocyte-surface antigens labelled with technecium-99m (^{99m}Tc-HIG) and by radiolabelled anti-TNF monoclonal antibodies both being highly accurate in detecting joint synovitis (15, 16).

Nevertheless, although nuclear medicine investigations have become more specific with the introduction of these new methods, their use is still limited due to cost and availability in various centers as compared to the use of ^{99m}Tc-NC.

In the present study we examined a cohort of RA patients in clinical remission in order to find out whether clinical and laboratory parameters are consistent with the actual inflammatory activity in the joint assessed by ^{99m}Tc-NC scintigraphy.

Patients and methods

Patients

Forty patients from a large cohort of RA patients attending the rheumatology outpatient clinic of Asaf Harofe Medical Center were randomly selected. All patients signed an informed consent and the study was approved by the Ethics Committee of the Hospital. Patients were offered to participate in the study if according to the clinical judgment of their consultant rheumatologist they were in clinical remission.

Patients were included if they fulfilled the following criteria;

1) RA diagnosed according to the ACR criteria;
2) Disease duration of more than 2 years;
3) No disease flares in the preceding 6 months period;
4) No change of therapy for the past 6 months.

All patients had to satisfy both the preliminary ACR criteria for remission (15) and the DAS28 criteria for remission (DAS <2.6).

Demographic and clinical characteristics including age, sex, RA history, presence of RF, current and previous use of DMARDs, biologics and duration of remission, were obtained from patients' medical records.

A complete blood count and biochemical tests as well as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were taken within a two-weeks period prior to study examination.

A subgroup of 10 patients and of the study cohort who had clinical and radiological signs of secondary osteoarthritis associated with RA served as a control group. These patients were chosen in order to assess earlier findings that ^{99m}Tc-NC is a reliable tool in detecting active joint disease (11).

Methods

Patients had spot views and SPECT of the wrists and palmar joints 1 hr after an intravenous injection of 555MB1 (15 mCi) of ^{99m}Tc-nanocolloid, on a parallel-hole collimator.

A 20% window was set at 140 Kev. The spot views were performed for 5 min on a 256×256 matrix or for a total of 50 K Counts at zoom 1. The SPECT study was performed at 10 second per frame, 120 projection with 128×128 matrix and zoom 1.

Two nuclear medicine physicians read the scans independently and graded them as either: negative or positive. Differences in evaluation were resolved after reviewing the images together. Scan visual interpretation was carried out while blinded to any laboratory or clinical data.

A scan was considered positive when the scan showed increased tracer uptake in the joint, irrespective of the number of positive joints.

A scan was considered negative, when the scan showed diffuse tracer activity with no focal joint uptake.

Table I. Clinical and laboratory data of the study group.

Variable	Study group (n=40)	Control group (n=10)	*p*-value
M/F ratio	29/40 (72%)	8/10 (80%)	N.S.
Age (yrs.)	60.8 ± 13.5	65.3 ± 12.6	N.S.
(range)	(22 – 86)	(42 – 86)	
Disease duration (yrs.)	13.4 ± 7.7	15.2 ± 6.1	N.S.
(range)	(3 – 23)	(9 – 23)	
Disease remission period (months)	22.2 ± 5.2	19.8 ± 6.3	N.S.
(range)	(11 – 36)	(10 – 32)	
Positive RF.	27/40 (68%)	7/10 (70%)	N.S.
ESR (mm/h)	13.2 ± 5.3	12.6 ± 6.1	N.S.
CRP (mg/liter)	5.6 ± 4.1	6.2 ± 5.2	N.S.
Medication therapy			
MTX alone	25/40 (63%)	5/10 (50%)	N.S.
MTX + another DMARD	9/40 (22%)	3/10 (30%)	N.S.
Anti-TNF	6/40 (15%)	2/10 (20%)	N.S.

N.S.: non significant.
Values are presented as mean ± standard deviation.

Table II. Scintigraphy finding with ^{99m}Tc- nanocolloid.

Variable	Study group (n=40)	Control group (n=10)
Patients with scintigraphic pathology	24/40 (60%)	0/10 (0%)†
Frequency of imaging detected pathology		
wrists	21/40 (52%)	0/10 (0%)†
MCP's	14/40 (35%)	0/10 (0%)†
PIP's	7/40 (18%)	0/10 (0%)†

$^{\dagger}p<0.001$.

Results

Demographic and clinical features

A total of 40 RA patients who satisfied the preliminary ACR criteria for remission were studied. Thirty eight of them satisfied also the DAS28 criteria for remission (DAS<2.6). No patient had any swelling or signs of joint inflammation. The demographic and clinical features of the study group are presented in Table I.

The study population had a mean age of 60.8 years and was predominantly female (72%). Their mean disease duration was 13.4 years and they had a mean disease remission period of 22.2 months.

Positive RF was found in 68% of patients and they had a mean ESR of 31.2 mm/h and a mean CRP level of 5.6 mg/l.

All patients were receiving DMARD therapy and no patient was taking oral corticosteroids.

Most patients (63%) were taking methotrexate alone, and 22% were taking combination therapy – most of them methotrexate and hydroxychloroquine. Six patients (15%) were receiving therapy with biologic agents, all of them as monotherapy. No patient was receiving NSAIDs on a regular basis, but most of them were taking such drugs from time to time. The 10 control patients out of the study group had similar clinical and laboratory features as the study group.

^{99m}Tc-NC scintigraphy

The results of the scintigraphy finding are presented in Table II.

In the entire cohort of our RA patients, 24 patients (60%) had a positive ^{99m}Tc-NC positive scintigraphy. Pathology was mostly detected in the wrists

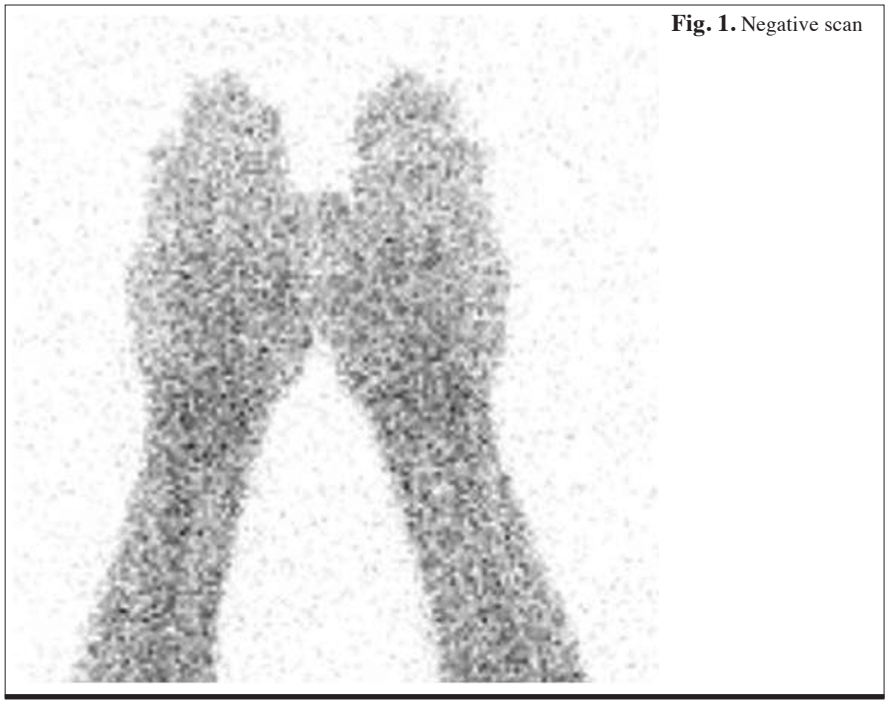

Fig. 1. Negative scan

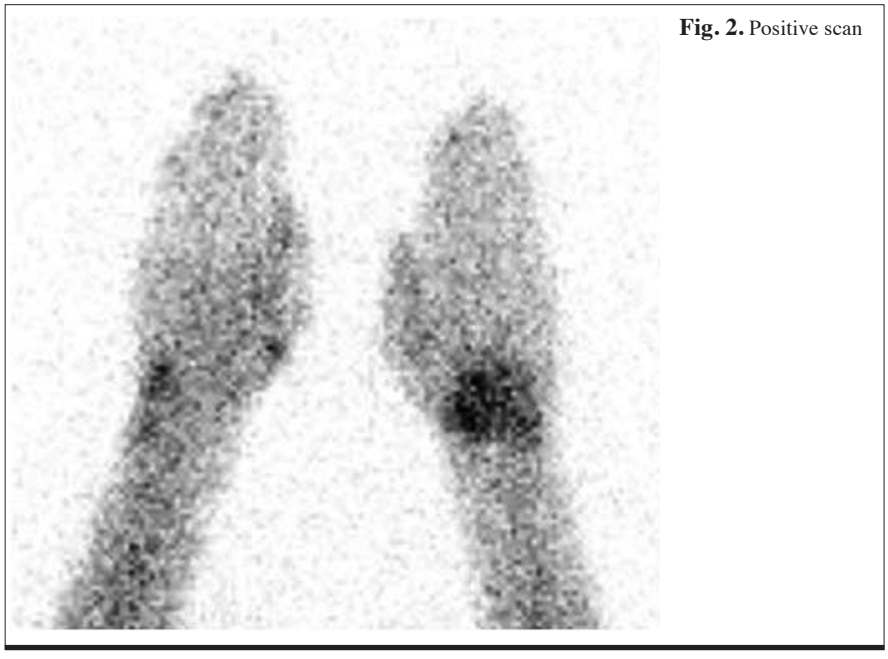

Fig. 2. Positive scan

(52%) followed by MCP's (35%) and PIPs (18%).

The presence of a negative planar scan is presented in Figure 1 while that of a positive scan is presented in Figure 2.

No discrepancies have been detected between planar and SPECT imaging.

Twenty four out of 26 patients (92%) with positive scans were sero-positive and only two patients were sero-negative. No other correlations with age, disease duration, disease remission period, ESR, CRP levels or medication therapy could be detected. No patient in the control group had evidence of radiolabelled nanocolloid accumulation in the joints with secondary osteoarthritis.

Discussion

Treatment in rheumatoid arthritis is directed towards reducing inflammation to a minimum and finally achieving a state of remission. The criteria used to detect remission are mainly clinical, but include also inflammatory laboratory variables (6, 17). Earlier studies have shown that even patients that fulfill the ACR and/or DAS28 remission criteria still demonstrate synovial inflammation on MRI and power Doppler ultrasound (8). Furthermore, recent studies have demonstrated that progression of radiographic joint damage continues in about 20% of patients despite being in clinical remission (18). These data suggest that the current methods used by us to assess disease activity or a state of remission are not sufficient and sensitive enough to detect a low level of ongoing inflammation in the joints. This happens in spite of the fact that both criteria ACR or DAS28 use inflammatory markers such as ESR and CRP as part of the evaluation (19).

In our study we have demonstrated for the first time that by using ^{99m} Tc-albumin nanocolloid joint scintigraphy in RA patients fulfilling both ACR and DAS28 criteria for remission, an active subclinical inflammation still exists. These results are in accordance with earlier studies that showed similar results by using different detecting methods, such as power Doppler ultrasound and Gadolinium-enhanced MRI (8, 18). In contrast to other methods used to detect synovitis, which can detect structural damage as well, the scintigraphic method used by us is merely functional and relates only to the activity of joint inflammation. This method has been found to be reliable and highly correlates with both dynamic and static MRI (13). Furthermore, we have shown, as did earlier studies, that uptake of ^{99m}Tc-albumin nanocolloid is specific for inflammation (10), since no patient with secondary OA in our group had a positive scan. The results of our study are unique because of the fact that 95% of patients in our study group fulfilled both remission criteria used today – those of the ACR and those of DAS28. Another interesting finding of our study which has not been addressed before is the fact that 92% of patients with positive scans were sero-positive. This finding is not surprising, since patients with a sero-positive disease usually present with a more aggressive disease that is difficult to control and causes erosive damage of joints affected (20). Further-

more, we found no correlation between the type of drugs used by the patients which included also anti TNF therapy and between the outcome of inflammatory process. However, the number of patients in remission was too small to draw significant statistical conclusions. We are aware that some limitations can cause a bias in interpreting our data and they include mainly the lack of updated conventional x-rays of hands, as well as the lack of the ability to compare our results with other modalities, such as power Doppler ultrasound and MRI.

Nevertheless, our study has important clinical implications concerning the questions posed by both patients and physicians about the essence of continuing treatment despite clinical remission. Our results that support earlier similar studies done with other modalities further explain the discrepancy between the fact that although patients are considered to be in remission, joint damage progresses (21). Therefore, it seems that plain radiographs accepted worldwide as a measure of assessing structural outcome in RA are not enough. Other modalities, such as power Doppler ultrasound, MRI and ^{99m}Tc-albumin nanocolloid should be used to evaluate disease activity. These results may also enhance researchers to modify the criteria used today for remission in RA to modern ones, which will include clinical, laboratory and imaging parameters.

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