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99mTc-interleukin 2 and 99mTc-HMPAO granulocyte scintigraphy in patients with inactive Crohn’s disease

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ABSTRACT

Crohn’s disease (CD) is a chronic inflammatory bowel disease that may involve the whole gut. A marked intestinal T cell and macrophage activation is a key feature of the disease. A polymorphonuclear cell infiltration is also observed in the diseased gut, mainly during active inflammation. Scintigraphic detection of granulocytes and activated lymphocytes infiltrating the gut wall may be useful in an attempt to identify a subgroup of clinically inactive patients undergoing early clinical relapse. Aims of the present study were to compare the scintigraphy with 99mTc-labelled IL2 (99mTc-IL2) and 99mTc-HMPAO labelled granulocytes (99mTc-WBC) in detecting the presence and the extent of bowel inflammation in patients with long-term inactive CD (>12 months) and to assess the accuracy of these techniques in predicting future disease relapse. We studied 29 patients with ileal and/or colonic CD in stable clinical remission (CDAI <150 for at least 12 months) both with 99mTc-IL2 and with 99mTc-WBC scintigraphy in order to evaluate the extent of acute and chronic inflammation in the bowel. Planar and SPET images were acquired for each patient at 1-hour p.i. For a quantitative analysis of 99mTc-IL2 uptake, the abdomen was divided in 32 ROI. Results showed that, despite the absence of symptoms, 18 patients (62%) showed a positive 99mTc-IL2 and 18 (62%) a positive 99mTc-WBC scan. Only 11 of these patients (37.9%) were positive to both scintographies, but the site of IL2 and granulocyte bowel uptake was different in most areas, indicating that in CD, acute and chronic inflammation can be located in different sites. As far as the prognostic role of both scans in predicting future disease relapse is concerned, both scans showed a high Negative Predictive Value (1.00 and 0.91, respectively), but a weak Positive Predictive Value (0.44 and 0.39, respectively). Nevertheless, Kaplan-Meier curves generated between scintigraphic finding and time free from disease relapse.
relapse were statistically different only for the $^{99m}$Tc-IL2 scintigraphy (log-rank test, $p=0.013$). These results indicate that $^{99m}$Tc-IL2 scintigraphy can be useful to select CD patients in clinical remission who could benefit of a preventive therapy to avoid disease relapse.

Key words: Crohn’s disease, inflammation, lymphocytes, granulocytes, Interleukin 2.

INTRODUCTION

Crohn’s disease (CD) is a chronic inflammatory bowel disease that may affect 1.9-6.6/100,000 patients every year in Italy [1]. Although the aetiology of CD is currently unknown, growing evidences suggest that a genetically determined inappropriate mucosal immune response towards antigens within the gut lumen, including the resident bacterial flora, plays a key role in the pathogenesis of the disease [2]. An increased number of T cells and macrophages within the gut lumen is a feature of CD and most of these cells are activated [2-4]. A cellular mediated immune response driven by cytokines secreted by T helper 1 cells (Th1) is observed in CD, with increased mRNA expression and release of interleukin 12 (IL12), interferon-γ (IFN-γ), interleukin 18 (IL18), tumour necrosis factor-α (TNF-α) by intestinal lamina propria mononuclear cells [2-6].

The clinical course of CD is characterised by recurrent episodes of relapse and by the post-surgical recurrence of the disease [7]. One of the main problems in clinical management of CD is the identification of patients undergoing early relapse for proper treatment and relapse prevention [8]. The follow-up of patients in clinical remission is currently based on the calculation of clinical activity indexes, including the Crohn’s Disease Activity Index (CDAI) [9], together with radiological and endoscopic studies. Several parameters, including serum levels of soluble IL2 receptors (sIL2R) [10], interleukin-6 (IL6) [11], C reactive protein (CRP) [12] and an increased intestinal permeability (lactulose/mannitol test, faecal calprotectin, faecal α1-anti-trypsin clearance) [13-15] have been proposed as indicators of disease relapse. However, no subclinical markers are currently available at this purpose. It is also a matter of debate whether the inflammation of bowel mucosa persists in patients with clinical remission and what is its relation with clinical disease relapse [16].

Scintigraphy with labelled white blood cells (WBC) has been successfully used in CD patients to detect abscesses, to assess the disease extent (particularly for the small bowel) and activity [17-19]. Nevertheless, its use in patients with clinical remission is controversial, since in these subjects the presence of a positive scan does not necessarily indicate a disease reactivation. WBC scintigraphy has also been reported as a sensitive (but not specific) technique for detecting the post-surgical asymptomatic recurrence of CD [20].

IL2 is a cytokine involved in T-cell differentiation and proliferation [21]. High affinity receptors are expressed mainly on activated T-lymphocytes and monocytes. In CD patients with clinically inactive disease, an increased “in vitro” release of TNF-α and IL1-β by intestinal lamina propria mononuclear cells has been associated to an early clinical relapse of the disease [22]. We
previously evaluated the role of scintigraphy with $^{123}$I-labelled Interleukin 2 ($^{123}$I-IL2) in patients with CD [23], showing that bowel $^{123}$I-IL2 uptake was higher in active CD patients, although several patients in clinical remission showed a positive scan. The extent of bowel $^{123}$I-IL2 uptake (expressed as number of positive intestinal areas) in patients with inactive disease inversely correlated with the time free of symptoms, therefore suggesting a role of this technique in the prediction of disease outcome [23].

New therapeutic strategies in this field, in particular the use of anti-TNF-α antibodies [24], aim to modulate or extinguish the local mononuclear cell infiltration in the gut. In this view, IL2 scintigraphy could be useful to monitor the efficacy of new therapies in a more objective way. In addition, it can be also useful to select patients in clinical remission who could benefit of a preventive therapy to avoid disease relapse.

Aims of the present study were to compare the scintigraphy with $^{99m}$Tc-labelled IL2 ($^{99m}$Tc-IL2) and $^{99m}$Tc-HMPAO labelled granulocytes ($^{99m}$Tc-WBC) in detecting the presence and the extent of bowel inflammation in patients with long-term inactive CD (>12 months) and to assess the accuracy of these techniques in predicting future disease relapse.

**MATERIALS AND METHODS**

**Patients**

33 patients with ileal or ileo-colonic CD, regularly attending the Gastroenterology Unit at the University of Rome "La Sapienza", were enrolled in the study. In all patients the disease was clinically inactive (CDAI<150) during at least the last 12 months. Only 29 patients (19 M and 11 F; mean age 47±10 years) completed the study follow-up. Two patients refused to perform the $^{99m}$Tc-WBC scan and two did not complete the follow-up. Diagnosis and follow-up of CD was made according to clinical, radiological and/or endoscopical and histological criteria [7, 9]. Patients had no concomitant liver or kidney disease, no pregnancy, no treatment with immunosuppressive drugs and inactive CD from at least 12 months before entering the study. The local Ethics Committee approved this study. All patients gave their informed written consent before entering the study.

**Clinical assessment and follow-up**

All patients were assessed for clinical activity by the CDAI score (remission: CDAI <150; activity CDAI ≥150) at 0, 6 and 12 months after scans or at time of relapse. The following routine haematological parameters were recorded in each patient at time of entry and after 6 and 12 months: eritrosedimentation rate (ESR), white blood cell count, red blood cell count, haemoglobin, haematocrit, platelet count, total proteins and/or serum albumin, C-reactive protein, orosomucoids. Antibodies anti-*Saccharomyces Cerevisiae* (ASCA) of both IgA and IgG subclasses were measured in serum of 24 patients by ELISA (Alifax, Italy). Soluble IL2R levels were measured in serum of 19 patients by ELISA (EuroClone, UK).
All patients received oral mesalazine (2.4-3 gr/day) during the study as maintenance therapy. Those patients who underwent clinical relapse during the follow-up have been treated using conventional protocols (steroids and/or other immunosuppressive drugs) and ended the study.

**Scintigraphy with $^{99m}$Tc labelled IL2**

Radiolabelling of IL2 was performed using a two-step technique as previously described [25]. $^{99m}$Tc-IL2 scintigraphy has been performed in each patient at entry. As controls, data obtained from 10 patients affected by cutaneous melanoma were used (age 37.2±6.5 years; range 28-50). Planar and SPET images of the abdomen were acquired 45 minutes after the injection of 3-5 mCi of $^{99m}$Tc-IL2. In order to quantify bowel radioactivity on SPET images, 2 consecutive transaxial sections (10 pixel thickness each) between the lower liver margin and the bladder have been reconstructed as previously described [23]. On each transaxial section, 32 squared Region of Interest (ROI) (5 pixels each) have been drawn over the gut and 1 circular ROI over the spine as background. Target to background radioactivity ratio (T/B) of the 32 squared ROIs was calculated.

**Scintigraphy with $^{99m}$Tc-labelled white blood cells (WBC)**

$^{99m}$Tc-HMPAO labelled granulocyte scintigraphy was performed in each patient at entry (3-7 days before or after $^{99m}$Tc-IL2 scintigraphy). A standard protocol was used to label purified autologous granulocytes with $^{99m}$Tc-HMPAO [26]. Briefly, granulocytes were isolated by sedimentation of 50 ml of blood (using acid citric dextrose as anticoagulant agent) added with 5% Hydroxy-ethyl starch, followed by density gradient centrifugation on Fycoll (Lymphoprep®, Nycomed, UK). Purified granulocytes were then labelled with $^{99m}$Tc-HMPAO (20-25 mCi), and injected intravenously (i.v.) into the patient (10-15 mCi). Planar gamma-camera images were acquired after 30 minutes, 1 and 3 hours. Bowel radioactivity was quantified in nine abdominal regions, as previously described [20].

**Statistical analysis**

Clinical remission was defined as CDAI <150; active disease as CDAI ≥150 at 0, 6 and 12 months. The delta CDAI scores ($\Delta$-CDAI) as the arithmetical difference between CDAI value at entry and at 6 ($\Delta$-CDAI-6) or 12 months ($\Delta$-CDAI-12) were also considered to evaluate disease worsening.

$^{99m}$Tc-IL2 intestinal uptake was expressed as follows:
1- qualitative judgement of planar views (positive/negative planar scan);
2- semi-quantitative analysis based on T/B ratios in the 32 squared ROIs from transaxial sections after SPET. A T/B ratio was defined positive if higher than the mean of control subjects + 2 SD in the same ROI. The number of positive ROIs in each transaxial section was also calculated.

Patients were classified as “positive” at $^{99m}$Tc-IL2 scan, if planar images showed bowel accumulation of radioactivity or if they had at least 3 positive ROI at SPET images.

$^{99m}$Tc-WBC intestinal uptake was expressed as follows:
1- qualitative judgement of planar views (positive/negative planar scan);
2- number of positive abdominal regions.
Patients were classified as “positive” at $^{99m}$Tc-WBC scan if at least 1 abdominal region showed bowel accumulation of radioactivity. Regression analysis was performed between the number of positive ROI at $^{99m}$Tc-IL2 or the number of positive bowel areas at $^{99m}$Tc-WBC scintigraphy and clinical as well as haematological parameters. The positive (PPV) and negative (NPV) predictive values of different parameters on the prediction of disease relapse were calculated. Kaplan-Meier analysis and log-rank test were applied to evaluate if the rate of disease relapses during follow-up were statistically different between patients positive or negative to $^{99m}$Tc-IL2 or $^{99m}$Tc-WBC scintigraphy. To compare statistical differences in haematological parameters between patients who did relapse or not, Student t test for unpaired data (quantitative data) or Chi squared test (qualitative data) were used.

RESULTS

Clinical relapse of the disease, as assessed by the CDAI values, was observed in 8 out of the 29 patients followed up for 12 months (27.6%).

$^{99m}$Tc-IL2 scintigraphy
Control subjects: None of control subjects revealed detectable abdominal uptake of radiolabelled IL2 on planar and SPET images.
Patients: Data analysis of planar and SPET sections were performed by two independent readers. Qualitative analysis of planar images resulted concordant in all cases. As far as the quantitative analysis of tomographic sections is concerned, a good correlation was observed between the two readers ($r=0.943; \ p<0.001$). Planar and SPET analysis of $^{99m}$Tc-IL2 scintigraphy in patients gave concordant results (table 1) and 18 out of 29 patients (62%) were classified as positive. In 1 of these patients planar images were not available. All patients who relapsed during the follow-up were positive to $^{99m}$Tc-IL2 scan, but 10 patients positive to $^{99m}$Tc-IL2 scan did not experience any disease relapse during the follow-up (table 1). Figure 1 shows a classification of patients in four groups.

![Figure 1: Classification of patients in four groups, on the basis of positivity/negativity to $^{99m}$Tc-IL2 (A) or $^{99m}$Tc-WBC (B) scan and the presence/absence of disease relapse during 1 year follow-up. Although the negativity to both scintigrapies is associated to disease stability and similarly the positivity with a possible relapse, many patients positive to one or both scan did not experience any disease relapse.](image-url)
This is based on the results of $^{99m}$Tc-IL2 (1a) or $^{99m}$Tc-WBC (1b) scan and their correlation with the disease outcome (relapse or not). The positive predictive value (PPV) for relapse was 0.44, the negative predictive value (NPV) was 1.00. Kaplan-Meier curves generated between scintigraphic finding and time to disease relapse showed significantly more relapse in patients with positive $^{99m}$Tc-IL2 scan (log-rank test, $p=0.013$) (figure 2a).

![Kaplan-Meier curves](image.png)

**Figure 2:** Kaplan-Meier curves showing the correlation between results of $^{99m}$Tc-IL2 (A) or $^{99m}$Tc-WBC (B) scintigraphy and percentage of patients free from disease relapse during follow-up. The curves with circles show the sub-groups of patients negative and the curves with triangles those positive to the $^{99m}$Tc-IL2 (A) or $^{99m}$Tc-WBC (B) scan.

A positive correlation was found between the number of positive ROIs and the Δ-CDAI-12 ($r=0.454$, $p=0.026$) (figure 3), but no significant correlation with $\Delta$-CDAI-6.
Figure 3: Correlation between N° of positive ROIs at $^{99m}$Tc-IL2 scan (analysis on SPET images) and $\Delta$-CDAI-12. A statistically significant correlation was found ($r=0.454$, $p=0.026$).

$^{99m}$Tc-WBC scintigraphy

Patients: Analysis of $^{99m}$Tc-WBC planar images revealed that 18 out of 29 patients studied (62%) showed a significant abdominal tracer uptake. All but one patient who relapsed during the follow-up had a detectable bowel uptake of $^{99m}$Tc-WBC. By contrast, 11 patients positive to $^{99m}$Tc-WBC scan did not show any disease relapse during the follow-up (table 1, figure 1b). The positive predictive value (PPV) for relapse was 0.39; the negative predictive value (NPV) was 0.91. Kaplan-Meier curves generated between scintigraphic finding and time to disease relapse did not show significantly more relapse in patients with positive than negative $^{99m}$Tc-WBC scan (log-rank test, $p=0.11$) (figure 2b). There was a positive correlation was between the number of positive areas and the $\Delta$-CDAI-6 ($r=0.454$, $p=0.017$) (figure 4), but no significant correlation with $\Delta$-CDAI-12.

Figure 4: Correlation between N° of positive abdominal areas at $^{99m}$Tc-WBC scan (analysis of planar images) and $\Delta$-CDAI-6. A statistically significant correlation was found ($r=0.454$, $p=0.017$).
Comparison between $^{99m}$Tc-IL2 and $^{99m}$Tc-WBC scintigraphy

Five patients were negative to both scans. Twelve patients were positive to both scans, but the uptake of the two radiopharmaceuticals was different in most bowel areas (figure 5).

Only one of these patients showed a co-localisation of the two tracers in the same inflamed areas (figure 6). Finally, 6 patients were positive to $^{99m}$Tc-IL2 and negative to $^{99m}$Tc-WBC (figure 7) and 6 were positive to $^{99m}$Tc-WBC and negative to $^{99m}$Tc-IL2 (figure 8). The PPV for disease relapse was higher if considering positivity to both scans (0.67).

Soluble Interleukin 2 receptors (sIL2R)
Serum levels of sIL2R were positive in 16 out of 19 patients. No correlation was observed between the presence of sIL2R and the disease outcome (PPV=0.31; NPV=0.33). Moreover, no significant differences in sIL2R titre were found between patients who did relapse or not (2501±1530U/ml vs 2735±2134U/ml; p=NS).

Antibodies anti-Saccaromyces Cerevisiae (ASCA)
ASCA IgA serum level was positive in 21 out of 22 patients, ASCA IgG in 8. No correlation between the antibody titre and the disease outcome was observed (IgA 37.44±13.5U/ml vs 38.15±26.94 U/ml; IgG 0.83±0.67 U/ml vs 1.03±0.67 U/ml; for patients with and without disease relapse, respectively; all p=NS).

DISCUSSION

Affected gut tissue in CD patients is highly infiltrated by activated mononuclear cells, as expression of a chronic inflammatory condition. Intestinal infiltration by polymorphonuclear cells (mainly granulocytes) is also observed, as expression of an acute inflammatory response. The sequence of events leading to chronic inflammation, as also to recurrent clinical flare-ups or to the development of new lesions at the peri-anastomotic area after resection of the involved gut, is still unknown. However, current evidences support that in CD gut, the persistence of activated T-cells and macrophages during remission may maintain and perpetuate the inflammatory process by releasing soluble mediators with pro-inflammatory activity (i.e. IL12, IFN-γ, IL18, TNF-α) leading to chronicity and to clinical flare ups of the disease [1-6, 8, 16, 22, 23, 27].

In order to test this hypothesis, in the present study we compared the extent of uptake of $^{99m}$Tc-IL2 and $^{99m}$Tc-WBC in clinically inactive CD patients and we also evaluated whether a high intestinal uptake may represent a marker of early clinical relapse.

$^{99m}$Tc-IL2 is a marker of lymphocyte-mediated, chronic inflammation by binding in vivo to activated lymphocytes and monocytes present in gut wall and in activated lymph nodes of affected gut [23, 28]. $^{99m}$Tc-WBC is a marker of granulocyte-mediated, acute inflammation and infection. Results from the present study showed that despite the long-term disease remission (>12 months) areas of acute and/or chronic inflammation may still be detected in some patients.
Figure 5: $^{99m}$Tc-IL2 (left) and $^{99m}$Tc-WBC (right) scan in a patient with CD in stable remission. Tracers accumulate in different bowel segments (IL2 mainly in the mesogastrium and WBC in the right iliac fossa and in the right flank, arrows) indicating that some segments are predominantly infiltrated by activated mononuclear cells and others by granulocytes.

Figure 6: $^{99m}$Tc-IL2 (left) and $^{99m}$Tc-WBC (right) scan in a patient with CD in stable remission. The two tracers accumulate in the same tract of terminal ileum, indicating the concomitant infiltration by activated mononuclear cells and granulocytes.

Figure 7: $^{99m}$Tc-IL2 (left) and $^{99m}$Tc-WBC (right) scan in a patient with CD in stable remission. A pathological IL2 uptake can be observed in the left flank and in the mesogastrium. The WBC scan is negative.

Figure 8: $^{99m}$Tc-IL2 (left) and $^{99m}$Tc-WBC (right) scan in a patient with CD in stable remission. A pathological uptake of radiolabelled granulocytes can be observed in a bowel loop localised in the right flank and hypocondrium. IL2 scan is negative.
Interestingly, in those patients in whom positivity to both scintigraphies is detectable (n=12), the areas affected by chronic and acute inflammation are usually located in different bowel segments. The observation that despite these findings all patients were clinically inactive (CDAI <150), supports the concept that a persistent active mucosal inflammation in the gut wall is present also in absence of overt symptoms related to CD [8, 16, 22, 23, 29].

The question is about the clinical significance of a positive scintigraphy in a patient with CD during a remission phase. We therefore examined the positive and negative predictive value of both scintigraphies for detecting a disease relapse. Both IL2 and WBC scan showed a similar high negative predictive value in excluding future early disease relapses. On the other hand, the PPV was 0.47 and 0.39 for $^{99m}$Tc-IL2 and $^{99m}$Tc-WBC, respectively, indicating poor predictive value for both tests, although the Kaplan-Meier curves between patients positive or negative to $^{99m}$Tc-IL2 and the time to disease relapse were statistically significant. Moreover, when the positivity to both scintigraphies was considered together, the PPV was higher (0.67).

We previously demonstrated that a higher intestinal uptake, as assessed by $^{99m}$Tc-IL2 scintigraphy, represent a useful marker for the prediction of future clinical relapse (CDAI>150) in patients with inactive CD [23]. In the present study, our previous data have been partially confirmed, and a positive correlation was found between the extent of chronic inflammation on $^{99m}$Tc-IL2 scan (expressed as n° of positive ROI) and Δ-CDAI-12. Indeed, as shown in figure 1, there is a subgroup of 10 patients positive to $^{99m}$Tc-IL2 scan who did not experience any disease reactivation during the follow-up.

Different hypotheses could be postulated to explain these different findings. First of all, the study population differs in the two studies. In our first study we selected patients with chronically active ileal CD undergoing frequent clinical relapses [23], at higher risk to develop relapse within the next 12 months. Differently, in the present study we enrolled patients with ileo-colonic CD, most of them showing stable remission (at least 12 months). In addition, a longer patient follow-up could be necessary to detect disease relapses in the long-term, in particular for bowel obstructions due to fibrotic reaction not associated to an active mucosal inflammatory condition. Finally, some false positive areas of accumulation could be potentially due to non-specific bowel excretion of the chelating agent used for $^{99m}$Tc conjugation to the cytokine that is excreted via the liver. Despite non-specific bowel excretion can not be ruled out, the presence of non-specific bowel activity detected in some control subjects appears only 2 hours after injection of the radiotracer and our imaging time was never exceeding 1h post-injection.

According to previous studies [30] we found that the WBC scintigraphy in patients with inactive CD is highly sensitive in detecting sites of acute inflammation, also in the absence of clinical symptoms. Similarly to IL2, the degree of WBC uptake may be useful for predicting future CD relapses. However, the finding that the degree of WBC uptake correlates with Δ-CDAI-6, suggests a shorter delay between inflammatory activity and the worsening of clinical conditions. WBC scintigraphy may be useful for addressing specific aspects of CD, including the detection of abscesses and fistulae, as a screening test in patients with suspect of IBD, as an adjunctive test for the differential diagnosis with ulcerative colitis and for detecting the early post-
surgical recurrence of CD [17-20]. Nevertheless, WBC scintigraphy currently plays a minor role in clinical management of CD patients, particularly in those with stable remission.

Results from our study, comparing for the first time results from IL2 and WBC scintigraphy in patients with CD, suggest the usefulness of both techniques and of IL2 scintigraphy in particular, in the long-term follow-up of patients with clinically inactive CD. Thus, a negative IL2 scintigraphy shows a high NPV value for disease relapse in the next 12 months, thus providing useful information for proper treatment of inactive patients. Although comparable statistical results were observed by using $^{99m}$Tc-WBC or $^{99m}$Tc-IL2 scintigraphy, 12 out of 29 patients (41%) had discordant results, indicating that both acute and chronic gut inflammation may be present asymptomatically in CD patients and be an early marker of clinical disease relapse. IL2 scintigraphy shows several advantages respect to WBC scintigraphy: it does not require any blood manipulation and the future development of a one-step labelling kit will reduce time and preparation costs. In the light of these results, we propose the use of $^{99m}$Tc-IL2 scintigraphy in the follow-up of CD patients in remission phase to be performed once a year. If scan is positive a WBC scintigraphy should also be performed to better characterise disease extent and severity. Patients with a negative IL2 scan seem to be free from disease relapse. Whether clinically inactive CD patients showing a persistent active mucosal inflammation within the gut wall, as detected by IL2 scintigraphy, need to be treated as active patients for possible prevention of disease relapse or complications, needs further investigations.

REFERENCES


**Table 1:** Summary of scintigraphic results and disease outcome

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* Patient refused to perform the WBC scan; ** Patient did not complete the follow-up; N.D. not done
Maria Luisa, 1987, “Senza titolo”