Nuclear gastroenterology: novel techniques in clinical and experimental gastrointestinal mobility, IBD and hepatology
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99mTc-HMPAO WBC scintigraphy in the assessment of the extent and severity of an acute exacerbation of ulcerative colitis

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory bowel disease with frequent exacerbations, including the risk for toxic megacolon and severe complications. In very active disease, colonoscopy should not be performed to assess the severity and the extent of the disease. The aim of the current study was to determine whether $^{99m}$Tc-HMPAO labeled white blood cell (WBC) scintigraphy could be used as an alternative for colonoscopy to determine the extent and the severity of the disease in critically ill patients.

**Methods.** Twenty consecutive patients (7F, 13M, age 38.1 ± 13.1 yr) who had a severe attack of UC underwent scintigraphy the day of admission. Leukocytes were labeled with 200 MBq $^{99m}$Tc-HMPAO. Planar anterior and posterior imaging of the abdomen was performed 45 and 120 min after WBC reinjection. The tracer uptake in the different colon segments was scored visually compared with bone marrow uptake. A symptom score was made and C-reactive protein was measured as a serologic marker of inflammation. Rectosigmoidoscopy with biopsy was performed within 24 h of scintigraphy. Scintigraphic, endoscopic and histologic results were compared for disease activity.

**Results.** The mean symptom score was 12.7 (± 0.7) on a scale of 21, and the mean C-reactive protein level was 6.8 (± 1.2) mg/L. No significant difference was found between the scintigraphic score of the rectum and the endoscopic or the histologic score. The best correlation was found with the latter ($r = 0.66$, $P < 0.01$). Based on the results of scintigraphy, disease involved the left side of the colon up to the splenic flexure in 10 patients. The other patients had pancolitis.

**Conclusion.** Disease severity can be determined adequately by planar WBC scintigraphy in patients with severe attacks of UC. Because the presence and severity of disease correlates well with endoscopic and histologic findings, it is possible to assess disease extent with WBC scintigraphy without the need for colonoscopy. This could decrease the number and severity of complications that can occur in already critically ill patients.
**Introduction**

Ulcerative colitis (UC) is a chronic inflammatory bowel disease accompanied by frequent acute exacerbations. It is usually diagnosed by rectosigmoidoscopy, colonoscopy or double-contrast barium enema.

Colonoscopic and contrast radiographic procedures have inherent disadvantages and can be cause of severe complications. In severe cases of the disease, colonoscopy should not be performed to assess the severity and the extent of the disease. Caution must be exercised in performing barium studies in acutely ill patients with severe colitis, because bowel preparation may worsen the disease or precipitate toxic dilatation of the colon. However, knowing the severity of disease is important for estimating the intensity of anti-inflammatory therapy and the risk of complications. Some recommendations for therapy are based on extent and severity of disease activity.\(^1^,^2\)

Despite convincing evidence in the recent literature about the potential benefits of \(^{99m}\text{Tc}\)-hexamethylpropylene amine oxime (HMPAO)-labeled leukocyte scintigraphy in adults,\(^3^,^7\) and children,\(^8^,^9\) the procedure is not performed routinely for UC in many hospitals.

The aim of the current study was to determine if \(^{99m}\text{Tc}\)-HMPAO labeled WBC scintigraphy can be an alternative to endoscopy with biopsy to determine the extent and the severity of the disease in these critically ill patients.

**Materials and methods**

**Subjects**

We included 20 consecutive patients (13 men, 7 women, mean age 38.1 ± 13.1 yr) with histories of UC who were hospitalized with severe exacerbations. Exclusion criteria were toxic megacolon or perforation evident on plain abdominal radiographs, infectious disease, and use of intravenous steroids for more than 12 h prior to admission. All
patients gave written informed consent to participate in the study, which was approved by the medical ethics committee of the Leuven University Hospital.

A clinical activity score was determined on admission. The C-reactive protein (CRP) was determined as a serologic marker of inflammation; levels ≥ 5 mg/L were considered abnormal. Rectosigmoidoscopy with biopsy was performed within 24 h of inclusion. Total colonoscopy was not considered appropriate in these patients. The macroscopic appearance of the mucosa was classified using a 4-grade scoring system. Mucosal biopsy specimens obtained in the most severely affected areas were also graded on a 4-point scale. All patients underwent scintigraphy within 24 h after endoscopy.
**Figure 2. Ulcerative colitis grade 2 pancolitis**

\textsuperscript{99m}Tc-HMPAO WBC scintigraphy of an ulcerative colitis patient with a grade 2 pancolitis. (A) Whole body image and (B) detail of the abdomen. Colon uptake has the same intensity as bone marrow uptake.

**Figure 3. Ulcerative colitis grade 3 pancolitis**

\textsuperscript{99m}Tc-HMPAO WBC scintigraphy of an ulcerative colitis patient with a grade 3 pancolitis. (A) Whole body image and (B) detail of the abdomen. Colon uptake is more intense than bone marrow uptake.
Figure 4. Ulcerative colitis mixed pattern

\(^{99m}\)Tc-HMPAO WBC scintigraphy of an ulcerative colitis patient with a grade 3 left sided colitis and grade 1 right sided colitis (A) Whole body image anterior (B) Whole body image posterior. Rectal uptake is clearly seen on the posterior image.

Scintigraphic test procedure

The technique of labeling granulocytes in mixed leukocyte suspension using \(^{99m}\)Tc-HMPAO (Amersham Health) has been performed according to the consensus protocol for leukocyte labeling.\(^13\) An average of 200 ± 10 MBq of \(^{99m}\)Tc-HMPAO labeled granulocytes was reinjected into the patient. Planar anterior and posterior 3-min images of the thorax, abdomen and pelvis were obtained at 45 and 120 min post reinjection using a large-field-of-view gamma camera (Bodyscan; Siemens Medical Solutions) fitted with a low-energy general-purpose collimator. Just before scintigraphy, the patient was asked to void.

The 45-min image was used subsequently for visual grading. Nonspecific bowel accumulation may occur on images obtained more than 60 min after reinjection.\(^14\) Therefore, the 120-min image was used solely to confirm the presence of lesions.
Scintigraphic data analysis. The scintigrams were evaluated by two physicians based on the knowledge of a normal distribution (Fig. 1) and without knowledge of the endoscopic, histologic, or clinical findings. Images of the bowel were divided into five segments (rectum, sigmoid, and descending, transverse and ascending colon). The inflammatory activity for each segment was graded on the 45-min image by comparing the intestinal uptake with that of vertebral bone marrow and bone marrow uptake of the iliac crest (grade 0 = no abnormal activity; grade 1 = abnormal activity with an intensity less than bone marrow; grade 2 = abnormal activity equal to bone marrow; grade 3 = activity more than bone marrow). Only the scintigraphic score of the rectum was used to evaluate disease activity, because endoscopy was restricted to the rectum and sometimes the distal sigmoid. Disease extent was evaluated for the entire colon using the scintigrams (Fig. 2-4). In all score (endoscopic, histologic and scintigraphic) interpretations, grade 0 indicated normal bowel mucosa and grades 1 to 3 indicated mild, moderate and severe disease, respectively.

Dosimetry. The radiation dose received by target organs – the spleen, liver and bone marrow – were 0.21 mGy/MBq, 0.025 mGy/MBq and 0.023 mGy/MBq, respectively. The effective dose equivalent was 0.011 mSv/MBq (ICRP-62).

Statistical analysis

All results are expressed as mean ± SEM values. The paired-samples t test was used to compare differences between activity scores. Spearman’s rank correlation was used for statistical analysis of results. All statistical tests were 2-tailed and differences were evaluated at the 5% level of significance.

Results

Inflammatory activity determined clinically using the numerical symptom score (0 indicating no symptoms, and a maximum score of 21 indicating severe symptoms) was 12.7 ± 0.7. Inflammatory activity determined serologically using the CRP had a mean value of 6.8 ± 1.2 mg/L. The endoscopic, histologic and scintigraphic score had a mean
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## Table 1. Patient data

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Endoscopic, histologic and scintigraphic score: grade 0 indicates normal bowel mucosa and grades 1 to 3 indicates mild-, moderate and severe disease, respectively.
**WBC scintigraphy in ulcerative colitis**

**Figure 5. Correlation between scintigraphic, endoscopic and histologic findings**

Correlation of activity score assessed by (A) histology and scintigraphy ($r = 0.66, P < 0.01$); (B) histology and endoscopy ($r = 0.37$); and (C) endoscopy and scintigraphy ($r = 0.13$). The straight line represents the line of equality.
value of $2.4 \pm 0.15$, $2.4 \pm 0.15$ and $2.5 \pm 0.14$, respectively (Table 1), representing moderate to severe disease overall. There was no significant difference between these 3 activity scores. Scintigraphy showed that all patients had pathologic uptake in the rectosigmoid, resulting in a sensitivity of 100%. Based on these scintigraphic findings, disease involved the left side of the colon in 10 patients. The other patients had pancolitis. There was no significant difference between the clinical score or CRP for left-sided or pancolitis. All abdominal lesions were continuous, involving the rectum and extending proximally. No skip-lesions were visible. Pathologic activity outside the abdomen was not detected.

We found a significant correlation between the scintigraphic and histologic indices of disease intensity of the rectosigmoid ($r = 0.66$, $P < 0.01$). The correlation between the endoscopic and histologic indices ($r = 0.37$) or the endoscopic and scintigraphic indices ($r = 0.13$) was not significant (Fig. 5).

**Discussion**

Soon after the introduction of labeled WBC scintigraphy, the first trials evaluating $^{111}$In labeled autologous leukocytes as a diagnostic tool for inflammatory bowel disease were conducted. The investigators concluded that this technique provides a rapid, simple, nontraumatic and effective technique for identifying the site of the inflammatory process in Crohn's disease and the extent of disease in ulcerative colitis. Ten years later, $^{99m}$Tc-HMPAO labeled leukocytes became available. The better imaging characteristics and the significant reduction of radiation burden were promising for further evaluation of $^{99m}$Tc-HMPAO labeled leukocytes. Prospective comparison of $^{99m}$Tc-HMPAO WBC's and $^{111}$In-labelled granulocytes showed that early imaging with $^{99m}$Tc-WBCs can reliably replace $^{111}$In-granulocyte scintigraphy for assessing the presence and localizing active disease in patients with possible exacerbations of inflammatory bowel disease (IBD). Research also showed that $^{99m}$Tc-WBC scintigraphy is superior to the activity index of van Hees and the gastroenterologist's clinical opinion for diagnosing active
WB CC scintigraphy in ulcerative colitis

inflammation in patients with IBD. The sensitivity and specificity are very high (94-100%) for active disease. In general practice, thorough history taking and repeated physical examination and scoring of clinical activity indices, complete with the findings of basic laboratory studies, allow the physician to make a diagnosis of relapse and determine the extent and severity in patients with a known history of UC. Endoscopy with biopsy is an important aid in the assessment of disease activity, but is limited for determining disease extent in patients with severe colitis. Furthermore, therapeutic follow-up and determination of remission should be as reliable as possible with minimal invasive testing. This might be less relevant in routine management in which follow-up can rely on clinical assessment, but it seems important in clinical trials seeking evidence of the therapeutic benefit of new drugs or strategies.

We used histologic findings from biopsy specimens obtained in the most severely affected areas in the rectosigmoid as the gold standard. The sensitivity of WBC scintigraphy for identifying rectosigmoidal involvement of UC in our series of selected patients was 100%, which is in accordance with the findings of other publications. The extent of disease was assessed only with scintigraphy in this study, because routine total colonoscopy and barium enema were not considered appropriate in these patients.

The correlation of a clinical index with other variables such as CRP, ESR, or endoscopic, histologic, or scintigraphic scores for extent and severity of disease is not always reported as significant. Clinical indexes have an inherent subjectivity, resulting in a less reliable activity score. Laboratory parameters like CRP and ESR reflect inflammation in general, and correlation with scintigraphic scores is not always significant in the literature. Given this perspective, an explanation for the lack of correlation between the clinical score or CRP with the scintigraphic extent and severity on planar imaging in this study seems speculative.

When histologic findings were considered the gold standard, scintigraphy yielded the best correlation. The correlations of histologic findings with endoscopic results and endoscopic findings with those of scintigraphy were inferior and not significant. These results confirm the role of scintigraphy in assessment of disease activity in patients with inflammatory bowel disease and ulcerative colitis in particular. False-negative results are
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reported, but seem to be restricted to low-grade activity, preferably in the rectosigmoid area. We had no false negative results of scintigrams for rectosigmoid disease in our study. This can be explained by the relative high-grade inflammation in our selected population, and careful preparation of the patient with voiding of the urinary bladder before scintigraphy.

Using computer-aided interpretation of leukocyte scintigraphy rather than a simple scintigraphic scoring system based on visual assessment of bowel activity has not been proven superior in determination of severity of inflammatory bowel disease.5

Previous reports confirm a significant correlation between scintigraphy and endoscopy for determining disease extent in patients in whom colonoscopy was not contraindicated.5-27.28 There is also a good correlation between scintigraphic uptake and macroscopic and histologic investigation of resection specimen.9 Thus, with the significant correlation in our series between scintigraphic and histologic findings of the rectosigmoid, we were confident to communicate disease extent in severe ill patients in whom colonoscopy was contraindicated.

The relative low radiation burden, achieved using 99mTc-HMPAO labeled WBC's, is not a contraindication for serial scintigraphy to monitor the response to therapy. Furthermore, the minimally invasive nature of the procedure is an advantage compared with other diagnostic methods.

Conclusion

Disease severity can be determined adequately by planar WBC scintigraphy in patients with a severe attack of ulcerative colitis. Because the presence and severity of disease correlates well with histologic findings, it is possible to assess disease activity and extent with WBC scintigraphy without the need for colonoscopy. This could decrease the number and severity of complications in already critically ill patients.
WBC scintigraphy in ulcerative colitis

References


