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Assessment of disease activity in inflammatory bowel disease: a new approach using ^{111}In granulocyte scanning

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Abstract

^{111}In leucocyte scanning yields images of diseased bowel in patients with inflammatory bowel disease. The technique has recently been improved by being made more specific for acute inflammation by the isolation and labelling of a pure granulocyte preparation. The value of ^{111}In granulocyte scanning in monitoring response to steroid treatment was assessed in 22 patients with Crohn's disease or ulcerative colitis. After steroid treatment there was agreement between the change in the scan grade and the change in clinical disease activity in 18 of the 22 patients. Overall there was a significant correlation between the change in the scan grade and clinical improvement ($r=0.775$, $p<0.001$).

This study suggests that ^{111}In granulocyte scanning can provide a rapid assessment of disease activity in inflammatory bowel disease.

Introduction

Drug treatment of inflammatory bowel disease is hard to evaluate because of the difficulty in assessing inflammatory activity.¹ Laboratory variables of inflammation, such as the erythrocyte sedimentation rate and C reactive protein and orosomucoid concentrations, are indirect and not specific for inflammation of the gut; thus they may be altered by extraintestinal complications or intercurrent illnesses. Direct assessment of the degree of bowel inflammation by radiological examination is an attractive approach for the clinician. Studies in both Crohn's disease^{2,3} and ulcerative colitis,⁴ however, have been disappointing, showing poor correlations between radiological

changes and response to drug treatment. Furthermore, recent studies have shown that considerable histological activity may be present—for example, in the colon—in the absence of radiological changes.^{5,6}

^{111}In leucocyte scanning has been used as an alternative to radiological examination for imaging inflammatory bowel disease⁷⁻⁹ and in principle should accurately show inflammatory activity. Recently, this technique has been made more specific for the acute inflammatory response by the isolation and labelling of a pure preparation of granulocytes distinct from lymphocytes and platelets.¹⁰ In this study we assessed the value of ^{111}In granulocyte scanning in monitoring the response of active inflammatory bowel disease to steroid treatment.

Patients and methods

Twenty two patients with active inflammatory bowel disease (Crohn's disease or ulcerative colitis) were studied before and after treatment with prednisolone 30-40 mg daily. The median duration of treatment was six weeks (range two to 16 weeks). Patients filled in a diary card, and a disease activity index was calculated¹¹ using the

FIG 1— ^{111}In leucocyte scans in case 2. Left: Before treatment, showing grade 3 activity in distal colon. Right: Normal scan after six weeks' steroid treatment.

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weighting factors derived in the National Co-operative Crohn's Disease Study.¹²

To avoid variations in the proportions of ¹¹¹In on the leucocyte, red cell, and platelet fractions a pure granulocyte preparation was separated out and labelled with ¹¹¹In tropolonate¹⁰ without being removed from the plasma. The dose of ¹¹¹In injected ranged from 150 to 300 μ Ci. Abdominal scans were performed two to four hours after reinjection of the labelled granulocytes and assessed independently by a nuclear physician and gastroenterologist according to the following grading system, which is based on the normal distribution of labelled cells—that is, with greatest activity in the spleen, intermediate activity in the liver, and least activity in the bone

Results

Initial and final assessments—Fifteen of the patients studied had Crohn's disease and seven ulcerative colitis (table). Fourteen were women and eight men. In all patients the disease activity index before treatment was greater than 150. Abdominal scans in all patients before treatment showed abnormal activity corresponding to grade 2 or 3 (fig 1 (left)). No patient had activity assessed as grade 4. After treatment activity scores were below 150 in 12 patients and the scan grade had changed to 0 or 1 in 13 patients. Overall there was a significant correlation between activity score and scan grade ($r=0.72$, $p<0.001$) (fig 2).

Clinical details of patients

Case No	Diagnosis	Distribution of disease	Disease activity index			Scan grade	
			Initially	Finally	Decrease	Initially	Finally
1	CD	Ileal	250	46	204	3	0
2	UC	Distal colon	305	102	203	3	0
3	UC	Pancolitis	323	40	283	3	0
4	UC	Pancolitis	320	141	179	3	0
5	UC	Pancolitis	240	43	179	3	0
6	CD	Ileal	241	130	111	3	1
7	CD	Ileal	239	90	149	3	1
8	CD	Ileocolonic	184	106	78	3	1
9	CD	Pancolitis	250	70	180	2	0
10	CD	Pancolitis	160	47	113	3	1
11	CD	Pancolitis	348	182	166	3	1
12	UC	Distal colon	327	192	135	3	1
13	CD	Ileal	331	232	99	2	1
14	UC	Pancolitis	307	175	132	3	2
15	CD	Ileal	278	103	175	3	3
16	CD	Pancolitis	242	160	82	3	3
17	CD	Pancolitis	256	230	26	3	3
18	CD	Ileal	202	187	15	3	3
19	CD	Ileal	202	101	101	2	2
20	CD	Pancolitis	249	157	92	3	3
21	CD	Pancolitis	312	296	16	3	3
22	UC	Pancolitis	320	272	48	3	3

CD = Crohn's disease.
UC = Ulcerative colitis.

FIG 2—Disease activity index versus scan grade before (●) and after (○) treatment ($r=0.72$, $p<0.001$).

FIG 3—Decreases in disease activity index and scan grade after steroid treatment ($r=0.775$, $p<0.001$).

marrow. Grade 0 indicates no abnormal activity; grade 1 indicates abnormal activity with an intensity less than or equal to that of bone marrow activity; grade 2 indicates abnormal activity with an intensity less than or equal to that of activity in the liver; grade 3 indicates abnormal activity with an intensity less than or equal to that of activity in the spleen; and grade 4 indicates abnormal activity with an intensity greater than that of splenic activity. Agreement between the two observers in assessing scan grade was 92.5%. In the remaining 7.5% of cases the scan grade was decided after discussion between the two observers.

Student's *t* test and linear regression were used for statistical analysis of results.

Effect of treatment—After steroid treatment 14 of the patients had improved, their scores of clinical activity having fallen by more than 100 (fig 3). Repeat study showed an improvement in scan grade in 12 of these 14 patients (fig 1); in the remaining two patients there was obvious improvement in the scan but this did not meet the criteria for a change in scan grade (fig 4). In two patients whose scan grade improved after steroid treatment the scores of disease activity fell by 99 and 78 respectively. The remaining six patients showed neither improvement in scan grade nor reduction in activity score by greater than 100. Overall there was a highly significant correlation between change in scan grade and change in activity index ($r=0.775$, $p<0.001$) (fig 3).

FIG 4— ^{111}In leucocyte scan in case 15. Left: before treatment, showing diffuse grade 3 ileal disease. Right: after two weeks' steroid treatment, showing considerable improvement but still grade 3 activity.

Discussion

^{111}In granulocyte scanning is a logical approach to the problem of assessing disease activity in inflammatory bowel disease. It has important advantages over clinical and laboratory assessments in being both a direct and a specific assessment of bowel inflammation, and it is accurate in determining the extent of disease in colitis^{7,11} and can detect complicating abscesses. The present work extends the usefulness of studies using labelled granulocyte in the overall assessment of inflammatory bowel disease.

The present technique offers several advantages over mixed leucocyte preparations. A granulocyte preparation allows the dosage of radioactivity to be reduced by up to half by avoiding unwanted red cell, lymphocyte, and platelet contamination, which increases background to target organ activity. Use of ^{111}In tropolonate to label granulocytes in plasma permits rapid visualisation of inflammatory sites,¹³ with accurate localisation within three hours after reinjection rather than the 16–24 hours used by other workers.^{12,14} In addition to shortening the time for investigation early scanning avoids the errors in determining disease distribution consequent on delayed scanning, when intraluminal transit of activity has occurred.

A major difficulty in evaluating a new assessment of disease activity in inflammatory bowel disease is the lack of an accepted "gold standard." The Crohn's disease activity index is useful as it is the most widely used clinical assessment against which newer clinical and laboratory assessments have been compared. Since many of the variables that are measured to obtain the index are also major indicators of disease activity in ulcerative colitis it should be applicable to assessing activity in ulcerative colitis.¹¹ It has certain limitations, however, the most serious being the high subjective element, which may be particularly important when drugs such as steroids with known euphoriant effects are being assessed. Furthermore, factors such as fibrous strictures and bowel resections can raise activity scores and not reflect inflammatory activity. In the present study scanning provided objective support to clinical scoring by showing active disease of grade 2 or more in all 22 patients. Scanning, however, also highlighted the limitations of the disease activity index in defining remission. In six (all with Crohn's disease) of the 12 patients with scores of less than 150 after treatment who therefore met the criteria for clinical remission¹² scanning showed inflammatory activity of grade 1 or higher. A grade 0 scan is therefore an alternative to the clinical definition of remission. Whether a treatment protocol designed to have an end point of remission on scanning would result in a more prolonged remission is uncertain, but such a policy merits investigation.

Although overall there was a surprisingly high correlation

between a change in the scan grade and a change in the disease activity index, the use of only four grades of activity on scans means that small changes in activity cannot be detected. Computer linked analysis might improve the accuracy of the technique, but many centres do not have these extra facilities. An alternative modification is to measure faecal excretion of ^{111}In labelled granulocytes, which gives a more accurate and sensitive assessment of inflammatory activity.¹⁸ Scanning, however, is rapid and avoids all the problems associated with faecal collection.

^{111}In granulocyte scanning has the advantage over both radiological and endoscopic assessment in requiring no bowel preparation, being able to image both the small and large bowels in one examination, and by its safety even in severely ill patients. Furthermore, interpreting such scans is simple as an abnormality represents active inflammation, whereas in radiology it is often difficult to decide whether an abnormality represents active inflammation or chronic changes. These factors have encouraged several centres to use ^{111}In leucocyte scanning in inflammatory bowel disease, and already promising results have been reported in both adults¹⁶ and children.¹⁷

On the basis of this study we believe that ^{111}In labelled granulocytes offer important advantages over the standard mixed leucocyte preparations, and this technique should permit rapid, simple, and precise assessment of disease activity in inflammatory bowel disease.

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