Leading article

Labelled leucocyte scintigraphy in inflammatory bowel disease: clinical applications

Labelled leucocyte imaging is an established technique for the detection of inflammation and sepsis. Of the many radioisotopes used to label leucocytes, Indium-111 trypolone (111In) and Technetium-99m hexamethyl propylene amine oxime (99mTc HMPAO) are the most widely used. Leucocytes are obtained from heparinised, peripheral venous blood (40–100 ml) and then separated from erythrocytes and platelets by sedimentation with hydroxyethyl starch. Cell labelling is achieved by incubation with the radioisotope in plasma (or saline). After washing, the labelled leucocytes are injected intravenously and serial images are obtained using a gamma camera. 111In labels and remains firmly bound to all cells in mixed leucocyte suspensions. The use of pure granulocyte preparations probably reduces background activity and improves the image quality. 99mTc HMPAO initially binds to all blood cells but subsequently elutes from platelets and red cells leaving labelled granulocytes behind. 99mTc HMPAO is therefore considered a selective granulocyte label even when mixed leucocyte preparations are used.2 3 After injection, the labelled granulocytes marginate and then migrate into the inflamed lesion before being shed into the bowel lumen.

Serial imaging is important to distinguish luminal from bowel wall activity. With 111In images are most often obtained at three to four hours.4 Forward migration of luminal radioactivity5 makes late (24 hours) scans of little value, except when the technique is used to detect sepsis, for which late imaging is required. After 99mTc HMPAO imaging at 30–60 minutes and at two hours is preferable.3

The technique of labelled leucocyte imaging has been used to detect abscesses and other inflammatory lesions in which there is heavy granulocyte accumulation. Mucosal infiltration with leucocytes is a characteristic histological feature in inflammatory bowel disease particularly during periods when the disease is active. Labelled leucocyte scanning has been used in the global assessment of patients with IBD, with encouraging results. In this article we examine the role of this non-invasive technique in the management of patients with ulcerative colitis and Crohn's disease.

Assessment of disease extent

Assessment of disease extent in inflammatory bowel disease is central to the planning of treatment, particularly when surgery is being considered, for patient selection in clinical trials, and for cancer surveillance in ulcerative colitis. Both barium enema and colonoscopy with mucosal biopsy are traditionally used to evaluate the distribution of colonic disease. Colonoscopy is generally regarded as better than barium enema in providing direct and comprehensive assessment of colonic disease.6–8 Barium enema is less sensitive and can overlook extensive disease.6 9 Pending developments in enteroscopy, small bowel barium studies remain the first choice for the detection of small bowel disease. When small and large bowel disease is suspected, both radiological examinations are required to determine the extent of disease. Colonoscopy and barium radiology are not popular with patients. They are time consuming, uncomfortable, and require bowel preparation with purgatives. Both techniques are poorly tolerated and are inappropriate in severely ill patients with inflammatory bowel disease.

Several studies have examined the role of labelled leucocyte scintigraphy in the assessment of disease extent in patients with established inflammatory bowel disease.10–20 Both 111In and 99mTc HMPAO bowel imaging have been compared with other methods used to assess disease extent including barium radiology,10 11 14 24 28 colonoscopy,13 21 23 26 27 surgery, or frequently a combination of these.12 15–20 22 25 29 Studies which compared 111In with barium enema and colonoscopy have given conflicting results. Complete agreement between 111In imaging and barium enema in patients with colonic disease is achieved in 70–90%,10 11 14 24 When 111In was compared with colonoscopy and histology, however, concordance rates of only 13–62% were obtained.13 21 23 Concordance rates of 35%–95% have been reported when 111In has been compared to a combination of radiology and endoscopy.12 15–20 22 99mTc HMPAO seems more accurate than 111In in assessing disease extent, with concordance rates of 59%–100% reported in comparison with other reference methods.25–29 The accuracy of bowel imaging in assessing disease extent depends upon the presence of active disease. Most studies have shown that patients with quiescent or mildly active disease are more likely to have a negative labelled leucocyte scan.10 11 15 20 In contrast, high concordance rates (90–95%) between bowel scintigraphy and radiology and endoscopy have been shown in patients with active disease.14 20 22 26 28 29

Leading articles express the views of the author and not those of the editor and the editorial board.
When the aim of labelled leucocyte bowel imaging is to detect active colonic inflammation regardless of its precise location, the technique has a sensitivity, specificity, and diagnostic accuracy of 65%-100%, 50%-100%, and 37%-95% respectively compared with endoscopy and radiology. Differences between studies in the proportion of patients with active disease are a major factor in determining the wide variations in the reported sensitivity and accuracy of \(^{111}\)In scanning. Similar results have been reported with \(^{99m}\)Tc HMPAO, although identification of various bowel segments is improved because of better image quality.\(^{25-29}\)

The role of labelled leucocyte imaging in the evaluation of small bowel disease is uncertain. Many studies have shown that \(^{111}\)In labelled leucocyte scanning has a sensitivity of 70% compared with small bowel radiology.\(^{17,30}\) When used to assess small bowel disease, \(^{111}\)In has a high false negative rate which reduces its diagnostic accuracy.\(^{17}30\) Although negative \(^{111}\)In scans are often obtained from patients with inactive disease, there are worrying reports of negative scans in patients with unequivocally active small bowel inflammation.\(^{25-29}\) Bowel uptake of \(^{99m}\)Tc HMPAO is better than those obtained with \(^{111}\)In. Scholmerich et al\(^{25}\) indicated that results from small bowel radiology in patients with terminal ileal disease compared favourably with those obtained from \(^{99m}\)Tc HMPAO scanning. Kennan et al\(^{28}\) found good correlation between \(^{99m}\)Tc HMPAO and barium studies in 14 out of 18 patients with small bowel Crohn’s disease.

One of the main disadvantages of labelled leucocyte bowel imaging compared to radiology and endoscopy is the difficulty in identifying various bowel segments, particularly in patients who have previously undergone bowel resection. This has been attributed to many factors including late imaging, absence of landmarks on bowel images, and the continuous movement of the small bowel during imaging. Thus, earlier imaging (within one hour) which minimises small bowel movement and better image quality with \(^{99m}\)Tc HMPAO allow improved definition of affected bowel segments.

Because of safety and convenience, labelled leucocyte imaging may be the investigation of choice in the assessment of severely ill patients with inflammatory bowel disease in whom other diagnostic tests such as colonoscopy and radiology are contraindicated. The technique may identify associated complications such as sepsis in addition to providing details of disease extent.

**Assessment of disease activity (severity)**

Recurrent exacerbations are the hallmark of inflammatory bowel disease. Effective treatment depends on accurate assessment of the severity of these exacerbations as well as the detection of associated complications and other non-inflammatory conditions which may present with similar symptoms. Accurate assessment of disease activity is also essential for the selection of patients for clinical trials and in monitoring the effects of drug treatment. An ideal measure of disease activity should be specific, objective, reproducible, and respond quickly to changes in clinical condition. Unfortunately, none of the existing measures fulfils these goals. Indices constructed from clinical observations\(^{30-33}\) are subjective and measurements, though objective, are not specific.\(^{40-42}\) Endoscopy and radiology are of limited value in the short term evaluation of changes in disease activity, and the frequency with which they can be repeated in the individual patient is limited.

Labelled leucocyte bowel scintigraphy in inflammatory bowel disease is of particular value in assessing disease activity. Two methods have been described for the quantification of the abnormal bowel uptake on the gamma camera scans – a simple visual grading system whereby the intensity of bowel activity is compared with that of bone marrow, liver, and spleen\(^{13}\)16 16 32 33 and, secondly, more detailed computer based methods with or without background subtraction.\(^{24,43}\) Bowel uptake, when quantified by visual or computer methods, has been shown to correlate with clinical indices\(^{12}\)16 25 32 43 44 and endoscopic and histological assessments.\(^{13,31,33}\) Correlations with laboratory measurements such as the sedimentation rate (ESR) and the C reactive protein (CRP) value are controversial.\(^{14,18}\) 25 29 31 While the visual grading method may be useful for a ‘rapid’, bedside assessment of disease activity it is largely subjective. When three independent observers graded \(^{99m}\)Tc HMPAO scans visually, complete agreement was achieved in only 9% of cases.\(^{45}\) An interobserver variation of up to 50% has been reported with visual grading.\(^{46}\) The computer based technique is cumbersome to design but is objective and has been used to define clinical remission, and to monitor the effects of treatment in small bowel Crohn’s disease.\(^{46}\)

Separation of active and inactive inflammatory bowel disease can be achieved with labelled leucocyte imaging with a sensitivity of 96%, a specificity of 98%, and accuracy of 98%.\(^{47,48}\) This is particularly useful in excluding active inflammatory infection in symptomatic patients with inflammatory bowel disease in whom symptoms may result from other non-inflammatory conditions such as irritable bowel syndrome or fibrous strictures from Crohn’s disease. Thus, bowel imaging allows the selection of appropriate treatment.

A four day faecal collection for measurement of \(^{111}\)In excretion is the most widely applied technique for the assessment of disease activity in inflammatory bowel disease.\(^{11,13,15,49-55}\) Faecal \(^{111}\)In excretion (FIE) is expressed as a percentage of the injected dose of \(^{111}\)In. Results of faecal leucocyte excretion using pure granulocytes are generally higher than those obtained with mixed leucocyte preparations in all study groups.\(^{50}\) Normal individuals and those with irritable bowel syndrome excrete less than 2% of the injected dose of \(^{111}\)In while patients with inflammatory bowel disease may excrete up to 40%. Patients with active disease have a significantly higher FIE (1-4%40%) than those with inactive disease (0-2-19), p =0.001.\(^{50}\) Furthermore, white cell excretion increases with the severity of inflammatory bowel disease (mild disease (0-2-30), moderate (0-5-11), and severe (3-8-11)).\(^{11}\) FIE correlates well with inflammatory markers such as the CRP (r=0-72, p=0-001),\(^{11,50}\) ESR (r=0-73, p<0-001),\(^{49,50,53}\) and orosomucoids (r=0-369, p=0-009).\(^{49}\) Saverymuttu et al\(^{13}\) have shown that FIE correlates with endoscopic and histological scores (r=0-625, p=0-05), a finding later confirmed by Leddin et al.\(^{15}\) Correlations with clinical indices are variable with some investigators reporting positive correlation\(^{13,15}\) 50 53 while others found no correlation at all.\(^{49}\)

Occasionally, faecal excretion is normal, yet ‘active’ disease is evident on the gamma camera images.\(^{54}\) Although in many of these patients the bowel uptake is ‘mild’, there are circumstances in which there is clear discrepancy between the faecal excretion and the abdominal images. Imaging therefore is probably more sensitive for the detection of active disease than retension and excretion studies. Negative images, however, are often obtained from patients with quiescent disease who may have ‘slightly’ raised FIE.\(^{54}\) There is as yet no satisfactory definition of remission in inflammatory bowel disease. Physicians are often
Labelled leucocyte scintigraphy in inflammatory bowel disease: clinical applications

labelled leucocyte scintigraphy is particularly useful in the management of patients with Crohn’s disease who present with symptoms of small intestinal obstruction. Bowel imaging enables the differentiation of obstruction due to an inflammatory stricture, when medical treatment will be appropriate, from that due to fibrous stricture when surgical intervention will be required.

Screening for inflammatory bowel disease
Abdominal pain and altered bowel habits constitute over 40% of all referrals to gastroenterology clinics. Up to 60% of these patients have functional bowel disorders but because of considerable overlap in clinical and laboratory features a rigorous approach is often needed before inflammatory bowel disease can be confidently excluded. This may entail detailed radiological and endoscopic assessment.

Labelled leucocyte scintigraphy has been used as a screening test in patients with suspected irritable bowel syndrome. False negative images are the main problem with In scanning. Although this is rarely seen in symptomatic patients with active disease, it significantly reduces the diagnostic accuracy of the technique. Studies which included patients with chronic diarrhoea due to the irritable bowel syndrome as controls have shown low false positive rates with In In granulocyte imaging and FIE.

Labelled leucocyte scanning is better than bowel radiology and rectal histology when used as a screening test for inflammatory bowel disease. 99mTc HMPAO seems to be as sensitive as In for the detection of active inflammation but appears to have high false positive rate in patients with no evidence of inflammatory bowel disease.

Gibson et al recently questioned the diagnostic value of a positive 99mTc HMPAO scan in predicting intestinal inflammation in patients with a low probability of inflammatory bowel disease.

Thus the value of labelled leucocyte scanning as a screening test in patients suspected of having inflammatory bowel disease remains to be established. When used for this purpose 99mTc HMPAO is preferable because it is more sensitive for small bowel disease and produces better quality images. A negative 99mTc HMPAO scan in symptomatic patients virtually excludes inflammatory bowel disease, while a strong positive scan makes such a diagnosis likely. A few patients, mostly those with irritable bowel syndrome, may have ‘slightly’ positive scans in these diagnosis cannot be made from the scan appearance.

In or 99mTc HMPAO?
Stable labelling of granulocytes can be achieved with either In or 99mTc HMPAO, with comparable labelling efficiency and granulocyte recovery times. Whole body distribution of the two tracers is similar with early localisation to bone marrow, liver, and spleen. Significant renal, biliary, and non-specific bowel excretion of non-cellular bound 99mTc labelled hydrophilic complexes is frequently seen with 99mTc HMPAO, particularly on late images. Although this may make scan interpretation difficult, it can be circumvented by early (one hour) and serial imaging. The short half life of 99mTc HMPAO together with biliary excretion make faecal excretion studies impractical. Disease activity and extent must therefore be estimated from the abdominal images. 99mTc is, however, readily available and because of its physical characteristics is more suited to the gamma camera, producing images of superior quality. Granulocyte rich can selectively be labelled with 99mTc HMPAO in mixed leucocyte suspensions, obviating the need for granulocyte...
Anlaby higher separation, enema. The Royal 7.7 leucocytes for the inflammatory autologous granulocyte for the inflammatory autologous granulocyte to imaging the colon and small bowel disease. BMJ 1982; 285: 1255-7.


Labelled leucocyte scintigraphy in inflammatory bowel disease: clinical applications


Labelled leucocyte scintigraphy in inflammatory bowel disease: clinical applications.
M H Giaffer

*Gut* 1996 38: 1-5
doi: 10.1136/gut.38.1.1

Updated information and services can be found at:
http://gut.bmj.com/content/38/1/1.citation

**Email alerting service**

These include:
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Topic Collections**

Articles on similar topics can be found in the following collections
- Colon cancer (1547)
- Endoscopy (1003)
- Ulcerative colitis (1113)
- Crohn's disease (932)

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/