Role of molecular imaging in the management of patients affected by inflammatory bowel disease: State-of-the-art

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Abstract

AIM
To present the current state-of-the-art of molecular imaging in the management of patients affected by inflammatory bowel disease (IBD).

METHODS
A systematic review of the literature was performed in order to find important original articles on the role of molecular imaging in the management of patients affected by IBD. The search was updated until February 2016 and limited to articles in English.

RESULTS
Fifty-five original articles were included in this review, highlighting the role of single photon emission tomography and positron emission tomography.

CONCLUSION
To date, molecular imaging represents a useful tool to detect active disease in IBD. However, the available data need to be validated in prospective multicenter studies on larger patient samples.

Key words: White blood cell scintigraphy; Inflammatory bowel disease; Inflammation; [18F]-Fluorodeoxyglucose positron emission tomography/computed tomography; Molecular imaging

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Core tip: Inflammatory bowel disease (IBD) is a chronic granulomatous inflammatory condition, in which the integrity of the gut epithelium represents a major pathophysiological step. Although endoscopy and barium radiological examinations are the diagnostic "gold standard" for IBD, both techniques require a specific patient preparation, not always feasible or easily tolerated. Molecular imaging with single photon emission tomography and positron emission tomography seems to be a reliable, non-invasive, accurate and easily reproducible diagnostic tool, able to assess location, extent and activity grade of IBD. We here present the current state-of-the art of molecular imaging in the management of patients affected by IBD.

INTRODUCTION
Inflammatory bowel disease (IBD) is a chronic inflammatory condition, in which the integrity of the gut epithelium represents a major pathophysiological step. Both ulcerative colitis (UC) and Crohn's disease (CD) follow a relapsing and remitting course. As such, tools able to diagnose and manage patients affected by these conditions are highly relevant in clinical practice.

Endoscopy and barium radiological examinations are the diagnostic "gold standard" for IBD. Unfortunately, both techniques require a specific patient preparation, which is not always feasible and not easily tolerated. Specifically, endoscopy is an invasive procedure associated with increased risk of bowel perforation, if performed during the acute phase of disease. Moreover, it cannot study the deepest layers of intestinal wall and discover possible extra-intestinal alterations. Finally, in case of CD complicated by strictures, endoscopic exploration often remains incomplete, due to difficulties in going beyond narrowed bowel segments and in exploring the distal side of the strictures.

In this context, the need for a novel non-invasive, accurate and easily reproducible diagnostic tool, able to assess location, extent and activity grade of IBD, is crucial. Molecular imaging with single photon emission tomography (SPECT) and positron emission tomography (PET) seems to be promising, allowing for tracking molecular changes occurring before clinical manifestations.

We therefore aimed at presenting the current state-of-the-art of molecular imaging in the management of patients affected by IBD.

MATERIALS AND METHODS

Search strategy
A comprehensive computer literature search of the PubMed/MEDLINE and Web of Knowledge database was performed in order to find important original articles on the role of molecular imaging in the management of patients affected by IBD. Papers on future perspectives in the field and experimental data were also searched. The adopted algorithm was based on a combination of the terms: (a) IBD and (b1) "positron emission tomography" or "PET" or (b2) "single photon emission tomography" or "SPET" and (c1) diagnosis or (c2) prognosis or (c3) follow-up. The search was updated until February 2016 and limited to articles in English. The references of the included articles were hand-searched in order to find important original articles on the role of molecular imaging in the management of patients affected by IBD.
retrieved articles were also checked for additional studies as not to exclude possible interesting data.

**Article selection**

Studies investigating the role of SPECT and PET in patients with IBD were eligible for inclusion. Studies with at least 6 patients were selected. Review articles, articles not in the field of interest, single/double case reports and commentaries were excluded. Meta-analyses were retrieved to provide convincing data for the discussion. Also, abstracts or oral/poster meeting presentations were not included.

**RESULTS**

Fifty-five original articles were included in this review. Specifically, 10 studies were available on the role of SPECT and 19 on PET. Furthermore, 13 articles were retrieved on the role of molecular imaging in paediatric patients, and 13 articles provided interesting insight on experimental data in the field.

**SPECT**

Table 1 shows the selected studies on the role of SPECT in adult patients affected by IBD. The majority of the studies were based on the ability of $^{99m}$Tc-HMPAO-white blood cell (WBC) to diagnose the presence of IBD. Lachter et al. showed that $^{99m}$Tc-HMPAO-WBC scintigraphy can be useful for patients with CD, while it is not sophisticated for the diagnosis of UC. Some years later, Paredes et al. reported that patients with suspected recurrent IBD after surgery can be evaluated with $^{99m}$Tc-HMPAO-WBC scintigraphy as an alternative to ileoendoscopy. The single-injection technique used for the administration of LeukoScan simplifies the labelling techniques required for white cell imaging. Kerry et al. investigated $^{99m}$Tc-leukoscan and $^{99m}$Tc-white cell scan in suspected IBD in 22 patients. Planar $^{99m}$Tc-WBC images were acquired at 45 min and 2 h post-injection, while planar $^{99m}$Tc-leukoscan images were acquired at 1, 2 and 4 h post-injection and with a SPECT after 4 h. From a head-to-head comparison $^{99m}$Tc-WBC scan showed a better diagnostic accuracy in IBD patients than $^{99m}$Tc-leukoscan.

A direct comparison between the diagnostic performance of $^{99m}$Tc-HMPAO-WBC SPECT and planar images was performed in 2005 and 2011. These two studies comprised 22 and 99 patients, respectively and reported comparable results between planar and SPECT images regarding diagnostic accuracy. However, SPECT images provided a more detailed visualization of those IBD lesions which were located in critical sites, like terminal ileum (due to the relatively intense overlying background bone marrow activity in the sacro-iliac region), pelvic floor and rectum (because the rectal disease is covered by the intense overlying background activity which is often present in the bladder).

Some authors aimed to quantify the severity of IBD by means of different parameters, like in-house validated scintigraphic indices (SI) at $^{99m}$Tc-HMPAO-WBC scan or the stool radioactivity (defined as the disappearance of $^{111}$In-radiolabelled leukocytes from the spleen or from the whole body retention, as they migrate toward regions of inflammation). As a matter of fact, such semi-quantitative methods for the assessment of the severity of disease could be important for an objective evaluation of treatment response, although a more extensive demonstration of their usefulness lacks in the literature.

Van den Brande et al. investigated whether apoptosis in the intestine underlies the clinical benefit of anti-tumor necrosis factor (TNF) treatment in CD, performing real-time imaging of in vivo apoptosis by using $^{99m}$Tc-annexin V SPECT at baseline and 24 h after Infliximab treatment both in 2 models of murine experimental colitis and in 14 patients with active CD. The authors found a mean increase of 98.7% in colonic uptake of $^{99m}$Tc-annexin V in 10 of the 14 responding patients compared with 15.2% in non-responding patients ($P = 0.03$). Thus, the use of $^{99m}$Tc-annexin V SPECT may be envisioned in order to predict the response to Infliximab, given the correlation between the colonic uptake of $^{99m}$Tc-annexin V and clinical benefit of anti-TNF treatment. This bears important implications in the choice of the best therapeutic options, also by increasing the cost-effectiveness of Infliximab.

A new emerging radiopharmaceutical agent was investigated to image the presence of Interleukin 8-receptors (IL8-R), which are overexpressed by activated neutrophils into the intestinal wall of patients with IBD. Recently, Aarnitzen et al. evaluated the accuracy of $^{99m}$Tc-IL8-R SPECT in a prospective series of patients affected by IBD (15 with CD and 15 affected by UC). Sensitivity and specificity on a per-patient basis for the detection of active disease were 95% and 44% for $^{99m}$Tc-IL8-R scan and 71% and 70% for endoscopy, respectively. On a per-segment basis, sensitivity and specificity were 82% and 72% for $^{99m}$Tc-IL8-R scan, and 74% and 85% for endoscopy, respectively. The degree of $^{99m}$Tc-IL8-R uptake correlated with that of neutrophilic involvement in affected mucosa. As such, the authors showed that $^{99m}$Tc-IL8-R SPECT provides a novel imaging technique able to target neutrophil recruitment in the intestinal wall, especially in IBD exacerbations of moderate-to-severe degree. These encouraging results suggest to take advantage from $^{99m}$Tc-IL8-R imaging in future studies, as a biomarker to personalize treatment with immunomodulating drugs.

An overview of diagnostic performance of SPECT in the most relevant studies is reported in Table 2.

**PET**

**PET/CT performance in the diagnosis of IBD:**

Positron emission tomography with $^{18}$F-Fluorodeoxyglucose ($^{18}$F-FDG-PET) fulfills, at least partially, the required criteria for a non-invasive, accurate and easily reproducible diagnostic tool, able to assess location, extent and activity degree of IBD. Inflamed tissues, especially during the active phase of disease, are often characterized by a high uptake of $^{18}$F-FDG on PET
Moreover, other complications such as abscesses, fistulas, inflamed lymph nodes can be effectively detected [1-4,6,7,20,21]. In the latest 10 years, a handful of studies explored the role of $^{18}$F-FDG-PET, eventually fused with CT, in the evaluation of disease activity in patients with known IBD.

| Ref. | Year of pub | Journal | n of pts | Indication | Imaging technique | Gold standard | Conclusion |
|------|-------------|---------|----------|------------|------------------|---------------|------------|
| Lachter et al. | 2003 | Hepato-Gastroenterology | 46 | Diagnosis of suspected inflammatory bowel disease | $^{99m}$Tc-HMPAO planar scintigraphy | Histology |  |
| Kerry et al. | 2005 | Nuclear Medicine Communication | 22 | Diagnosis of IBD and comparison between $^{99m}$Tc-HMPAO and $^{99m}$Tc-Leukoscan | $^{99m}$Tc-HMPAO planar scintigraphy, $^{99m}$Tc-Leukoscan planar scintigraphy, $^{99m}$Tc-Leukoscan SPECT | Histology, Radiology |  |
| Biancone et al. | 2005 | Am J Gastroenterol | 22 | Comparison between $^{99m}$Tc-HMPAO planar and SPECT for the assessment of intestinal infiltration in CD | $^{99m}$Tc-HMPAO planar and SPECT | Histology | SPECT images may better discriminate between intestinal and bone marrow uptake, thus allowing a better visualization of CD lesions in the pelvis (especially for perianal and enterovesical disease). |
| Cheow et al. | 2005 | Eur J Nucl Med Mol Imaging | 30 | To quantify disease activity in IBD | $^{99m}$Tc-granulocytes planar scintigraphy and $^{111}$In-granulocytes planar scintigraphy | NA | A dedicated whole-body counting using $^{111}$In can be useful to quantify inflammatory disease, especially IBD |
| Van den Brande et al. | 2007 | Gut | 14 | To predict the efficacy of anti-TNF treatment in IBD | $^{99m}$Tc-annexin V | Histology | The uptake of $^{99m}$Tc-annexin V correlates with clinical benefit of anti-TNF treatment |
| Mota et al. | 2010 | World J Gastroenterol | 20 | To evaluate inflammatory activity in CD patients | $^{99m}$Tc-HMPAO | NA | Scintigraphy with radiolabeled HMPAO could be useful for the evaluation of intestinal activity in CD |
| Paredes et al. | 2010 | Journal of Crohn's and Colitis | 40 | To assess the accuracy of abdominal ultrasonography, $^{99m}$Tc-HMPAO in recurrent CD | $^{99m}$Tc-HMPAO | Histology | $^{99m}$Tc-HMPAO can be used in case of postsurgical recurrence in CD, in particular for those patients who reject endoscopic examination or for the assessment of neoterminal ileum |
| Hillel et al. | 2011 | Nuclear Medicine Communication | 99 | To compare planar and SPECT imaging in IBD | $^{99m}$Tc-HMPAO | NA | SPECT improves interoperator variability and probably sensitivity for IBD. The size of lesion suggest that planar images underestimates the extent of active disease |
| Aarntzen et al. | 2015 | J Nucl Med | 30 | To assess the accuracy of $^{99m}$Tc-CXCL8 SPECT to detect and to localize disease activity | $^{99m}$Tc-CXCL8 | Histology | $^{99m}$Tc-CXCL8 is a novel target for neutrophil recruitment to the intestinal wall, especially in moderate to severe exacerbations of IBD |

$^{18}$F-FDG-PET scan allows to simultaneous evaluate functional and morphologic aspects of disease, thus permitting discriminating between active and quiescent inflammation (Figure 1). The relatively recent addition of computed tomography (CT) to $^{18}$F-FDG-PET images, due to overexpression of glucose transporters on the surface of neutrophils and macrophages, offers additional information about disease location. Moreover, other complications such as abscesses, fistulas, inflamed lymph nodes can be effectively detected [1-4,6,7,20,21].
In 2007 Meisner et al. published the first prospective study on 12 patients with known and at least moderate IBD (7 UC and 5 CD) undergoing 18F-FDG-PET/CT. In this pilot-study, the correlation between active regions on PET scan and those found to be active based on clinical criteria (including colonoscopy and radiologic examinations results) was equal to 95.8% in UC and 81.3% in CD patients. Interestingly, the co-registration with CT was helpful for anatomical identification of different bowel segments in CD, especially in case of small bowel involvement and surgically treated patients, whereas PET alone considered adequate to accurately define anatomic regions in those patients diagnosed with UC.

One of the main limits of 18F-FDG-PET is represented by false positive cases due to physiologic uptake of the radiopharmaceutical in normal bowel, caused by the typically high turnover of intestinal mucosa, the presence of material in the lumen, bacterial flora, lymphoid tissue inside the mucosa, but mostly by the peristaltic activity of muscular layer and the physiologic collapse of bowel loops. However, these two latter factors can be effectively overcome by a proper distention of bowel segments through the administration of great amount of fluids, as in the case of PET/CT enterography. To reduce the number of false positive findings in the intestinal tract during a PET scan, Franquet et al. proposed to undertake a therapy with Rifaximine 2 d before the PET scan. In their paper, this patient preparation allowed to reduce the unspecific FDG uptake.

For the evaluation of patients with CD, Ahmadi et al. retrospectively studied 41 patients with known or suspected active disease of the small bowel, who underwent 18F-FDG-PET/CT enterography. Thirty patients presented a total of 48 pathological bowel segments on CT enterography, of which 38 (79%) also showed an abnormal 18F-FDG uptake. All pathological areas identified by 18F-FDG-PET/CT enterography corresponded to abnormal areas visualized on CT enterography. CT enterography score of activity and semi-quantitative PET parameters showed also a significant correlation ($P = 0.03$). In a prospective study Groshar et al. also explored the ability of 18F-FDG-PET to detect IBD and to assess its degree of activity. The authors compared 18F-FDG-PET to enterography in 28 patients with known or suspected active CD. Eighty-five abnormal segments were found in 22 patients, while the remaining 6 subjects had unremarkable finding both on PET and CT enterography. The authors found a significant difference in abnormal and normal segments in mean wall thickness, mean mural enhancement and maximum standardized uptake value (SUVmax, $P < 0.0001$). A good correlation was also found between SUVmax and wall thickness or mural enhancement measurements, both in the colon and ileum ($P < 0.00001$). SUVmax correlated well also with the grade of other CT enterography parameters used to detect active inflammation, such as parietal attenuation, perienteric fat attenuation and perienteric/pericolic hypervascularization ($P < 0.001$).

A pilot study also analyzed the diagnostic advantage of adding 18F-FDG-PET to CT enterography. The authors compared PET and CT enterography alone in 13 CD patients with clinically suspected active disease, using histology after surgery or biopsy performed during endoscopy as gold standard (in 6 and 7 patients, respectively). In 3 (23%) patients, 18F-FDG-PET allowed
to identify signs of active disease otherwise missed by CT enterography alone, including an enterocolic fistula in one patient. Both techniques were able to identify all bowel segments with at least a moderate activity. There was a significant correlation between both techniques and histology in the evaluation of disease activity.

In a prospective study, Das et al\textsuperscript{[1]} compared \textsuperscript{18}F-FDG-PET/CT and colonoscopy in 15 patients, affected by mild to moderate UC. \textsuperscript{18}F-FDG-PET/CT detected 66 involved bowel segments, whereas colonoscopy found 67 pathological regions, so that the detection rate of \textsuperscript{18}F-FDG-PET/CT was 98.5\% compared to colonoscopy. A significant correlation between the two techniques was also found in the definition of disease extent (κ = 55.3\%, \(P = 0.02\)).

\textsuperscript{18}F-FDG-PET was also compared to other imaging techniques, showing in many cases even better diagnostic performance. In 2012 Holtmann et al\textsuperscript{[1]} evaluated 43 patients with active CD, undergoing \textsuperscript{18}F-FDG-PET, ileo-colonoscopy and hydro-magnetic resonance imaging (MRI). A total of 241 bowel segments in the terminal ileum and colon were examined. Endoscopy detected inflammation in 80 of 241, while \textsuperscript{18}F-FDG-PET in 72 (sensitivity and a specificity of 90\% and 92.6\%, respectively). Conversely, hydro-MRI identified 53/80 inflamed segments with a sensitivity of only 66.3\% and a specificity of 99.4\%. Specifically, hydro-MRI displayed the lowest sensitivity but a 100\% specificity for all colon segments, while in the terminal ileum sensitivity and specificity were 100\% and 93.3\%, respectively (vs 86.4\% and 93.3\%, respectively, of \textsuperscript{18}F-FDG-PET). In the proximal ileum, \textsuperscript{18}F-FDG-PET and hydro-MRI had the same results in all cases, reaching identical sensitivity and specificity.

One of the main issues in CD patients is to distinguish the nature of strictures (predominantly inflammatory or fibrotic, or mixed), as they represent a common complication of CD and show a very high rate of recurrence after surgical resection. As such, it is crucial to discriminate those lesions likely to benefit from surgical treatment (the predominantly fibrotic ones) from those still medically treatable (the inflammatory ones). With this regard, some authors suggested a possible role for \textsuperscript{18}F-FDG-PET, although data are still limited and controversial\textsuperscript{[2,4,5]}. While Shyn and colleagues reported no significant difference in SUV\textsuperscript{max} between the strictures deserving or not a surgical resection, although in a small patient sample\textsuperscript{[21]}, Holtmann et al\textsuperscript{[22]} showed that both hydro-MRI and \textsuperscript{18}F-FDG-PET have very high accuracy in detecting and characterizing strictures.

Louis et al\textsuperscript{[23]} prospectively studied 22 patients with CD. Ninety-five ileal segments were comparatively analyzed by endoscopy and \textsuperscript{18}F-FDG-PET/CT, showing a significant correlation between CD endoscopic index (CDEI) and RSUV\textsuperscript{max} (the ratios of each positive-segment SUV\textsuperscript{max} over the SUV\textsuperscript{max} of the liver). In their paper, \textsuperscript{18}F-FDG-PET/CT detected and localized the vast majority of gastrointestinal segments with moderate to severe lesions (sensitivity for superficial ulcers, deep ulcers, and strictures was 84.4\%), allowing a non-invasive evaluation of the ongoing pathologic process in the gastrointestinal tract. Overall, \textsuperscript{18}F-FDG-PET/CT detected 35 of 48 endoscopically affected segments (sensitivity for the detection of endoscopic lesions 72.9\%). This study demonstrated an important role of PET/CT in detecting active intestinal disease beyond the mucosa. This ability is important because complications of CD such as strictures may develop despite the lack of mucosal lesions visible at endoscopy, and because the presence of extraenteric inflammation is widely recognized as an important prognostic factor in CD.

PET/CT enteroclysis has been suggested in several studies as a new promising approach. This technique essentially consists in a simple extension of CT enteroclysis and provides information both on morphological details and on the metabolic activity of the lesions. In a study by Das et al\textsuperscript{[24]}, PET/CT enteroclysis, as a single test, detected involvement of a significantly higher number of intestinal segments [total = 50, 23 in the small intestine and 27 in the large intestine, (\(P < 0.01\)) compared to conventional barium studies (16 segments of small intestine) and colonoscopy (17 segments of large intestine). Similarly, a prospective study by Lenze et al\textsuperscript{[25]} compared the performance of \textsuperscript{18}F-FDG-PET/CT enteroclysis, MR enteroclysis and trans-abdominal ultrasound in the detection of CD strictures and in the differentiation of fibrotic vs inflammatory ones, using invasive endoscopy and histology as reference. In 30 symptomatic patients endoscopy detected 37 strictures, both PET/CT enteroclysis and MR enteroclysis 30/37 (81\%) and ultrasound 25/37 (68\%). By combining two methods, the sensitivity increased: Specifically, it was reported to be 92\% when combining PET/CT and ultrasound and 89\% when combining MR and ultrasound or MR and PET/CT. However, the differentiation rates of the strictures nature was low and equal to 57\% for MR, 53\% for PET/CT and 40\% for ultrasound. Considering only inflammatory strictures, MR and PET/CT correctly classified 94\% and 83\% of them, respectively, vs 66\% depicted by ultrasound. By combining two methods (MR and ultrasound or PET/CT with ultrasound), all the strictures deserving surgical resection could be identified.

More recently, a retrospective study of Catalano et al\textsuperscript{[26]} investigated the role of \textsuperscript{18}F-FDG-PET/MR enterography in discriminating between inflammatory and fibrotic strictures associated with CD, by using "quantitative" methods. Nineteen patients surgically treated within one month from imaging were evaluated and the following parameters were recorded for each resected bowel segment: The "SI" on T2 weighted sequences, the "apparent diffusion coefficient (ADC)", the SUV\textsuperscript{max} and the values obtained by multiplying the first two parameters by SUV\textsuperscript{max} (SI × SUV\textsuperscript{max} and ADC × SUV\textsuperscript{max}, respectively). In the 19 patients evaluated, 33 stricture bowel segments were resected. Of these, 7 presented with predominant inflammation, 11 with predominant fibrosis and 15 with a mixed pattern. A significant difference among these three types of stricture was reported in SUV\textsuperscript{max} (\(P = 0.02\)).
had significantly higher SUL or moderate chronic inflammation. Semiquantitative obstructive symptoms. For referring gastroenterologists considering surgery of 8 seemed to represent the most accurate threshold. In their paper, although known or suspected IBD. In their paper, although clinico pathological findings and PET/CT findings in a small cohort of subjects with moderately active IBD (n = 5) undergoing FDG PET/CT before and after successful medical therapy.

Rubin et al[27] evaluated a cohort of ten patients with UC in a strictly defined remission state (at least six month). A total body PET/CT was performed. The bowel was divided in several areas of interest and the uptake of FDG was scored on 3 point scale compared to the liver uptake. PET/CT showed 90% specificity in assessing disease activity in UC quiescent patients, and allowed the choice of the most adequate therapy options. Interestingly, PET could identify residual inflammatory activity in the colon despite negative endoscopic, histologic, and clinical findings.

Lapp et al[28] demonstrated that PET/CT significantly aids in the clinical decision-making in selected patients with known or suspected IBD. In their paper, although used in a heterogeneous group of patients (four with CD, two with pouches, and one without IBD), PET/CT could effectively lead to the choice of an appropriate therapy in each patient and proved superior to currently available modalities (e.g., laboratory, CT, endoscopy). Jacene et al[29] determined single-pixel maximum standardized uptake value corrected for lean body mass (SUL\text{max}) on PET/CT for lesions potentially representing active bowel inflammation. Patients with severe chronic inflammation had significantly higher SUL\text{max} than those with mild or moderate chronic inflammation. Semiquantitative analyses of 18F-FDG uptake helped in distinguishing predominantly active inflammation from fibrotic strictures and muscle hypertrophy. Specifically, a SUL\text{max} cutoff of 8 seemed to represent the most accurate threshold. Interestingly, patients with predominantly active inflammation, underwent surgery closer to the time of PET/CT compared with those with predominantly fibrosis or muscle hypertrophy. This information may be helpful for referring gastroenterologists considering surgery vs medical therapy for patients with CD who present with obstructive symptoms.

In several papers, PET/CT was reported to be superior to other standard radiologic or endoscopic pouch evaluations in the assessment of the response to treatment. Kuwaki et al[30] investigated 12 patients with CD undergoing granulocyte/monocyte apheresis (GMA). The response to treatment was monitored by measuring standard laboratory tests, CD activity index (CDAI) score, International Organization for the Study of Inflammatory Bowel Diseases score and regional and global bowel uptake on FDG-PET (baseline, at the 5th and at the 10th session of GMA). In 6 of 12 patients, a significant correlation was found between clinical and CDAI improvement and FDG uptake reduction vs baseline scan. As such, longitudinal changes in FDG-PET uptake in the involved bowel areas is of potential clinical value for assessing both regional and global bowel disease activity in CD patients during GMA therapy.

Other semiquantitative parameters of FDG PET/CT were investigated by Saboury et al[31] in order to determine the feasibility and potential clinical utility of this technique in the assessment of therapy response in CD. In a cohort of 22 subjects with CD in treatment undergoing 18F-FDG-PET followed by ileocolonoscopy and laboratory assay of Fecal Calprotectin and C-reactive protein (CRP), the authors searched for correlation between the global PET quantification measure (GCDAS, global SUVs) with CDAI, fecal calprotectin, CDEIs, and CRP level. A significant correlation was demonstrated between SUV\text{max}, PVC-SUV\text{max}, and PVC-TLG and CDEIS. Similarly, GCDAS was significantly correlated with CDAI and fecal calprotectin. As such, disease activity was effectively monitored through these semiquantitative parameters, allowing for a tailored treatment.

Molecular imaging in paediatrics

An overview of the selected studies on molecular imaging in paediatric patients is shown in Table 5.

Diagnosis: Planar scintigraphy and SPECT: As for adult patients, leukocyte-labelled scintigraphy is a useful tool in the diagnosis and therapeutic strategy of IBD, providing information on the presence, the activity and the extent of the disease, particularly in the terminal ileum[32]. Charron et al[33] reported a large series of paediatric IBD patients evaluated by 99mTc-HMPAO-WBC scintigraphy. One hundred and thirty-two patients with IBD were included, along with 52 patients with nonspecific gastrointestinal symptoms and a low probability of IBD and 31 healthy controls. Images were analysed considering bowel activity in 8 segments and scored using a 6-point scale based on liver, spleen and bone marrow uptake. 99mTc-HMPAO-WBC scintigraphy was proven useful in assessing the extent and distribution of inflammation [sensitivity 90%, specificity 97%, positive predictive value (PPV) 97%, negative predictive value (NPV) 93%, overall accuracy 93%]. Caobelli et al[34] found a correspondence between severity of inflammation as assessed by means of Mayo Score and uptake intensity (Scan Activity Index) in 87%
of patients and a full correspondence of location and severity of lesions in 15/16 patients. Overall, reported sensitivity and specificity for $^{99m}$Tc-HMPAO-WBC scintigraphy were 94% and 86%, respectively. On the other hand, other authors found a good correlation between scintigraphy and endoscopy for the intensity of inflammation ($r = 0.70$) but a poor correlation regarding the number of involved segments ($r = 0.30$), due to a significantly higher sensitivity of endoscopy as compared with scintigraphy$^{35}$. $^{99m}$Tc-HMPAO-WBC scintigraphy may distinguish discontinuous from continuous colitis with very good results$^{36}$.

### Table 3  Overview of the selected studies on the role of positron emission tomography in diagnosing inflammatory bowel disease

| Ref.            | Year of pub | Journal                  | n of pts | Indication                                                                 | Imaging technique                                                                 | Gold standard                                                                 | Conclusions                                                                 |
|-----------------|-------------|--------------------------|----------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Meisner et al$^{34}$ | 2007        | Inflamm Bowel Dis        | 12       | To identify regions of active inflammation in patients with known and at least moderate UC or CD | $^{99m}$Tc-FDG-PET/CT                                                          | Clinical evaluation including colonoscopy and radiologic imaging                | There is high correlation between $^{99m}$Tc-FDG-PET activity and clinical disease activity |
| Das et al$^{32}$  | 2010        | Eur J Nucl Med Mol Imaging | 15       | To assess the extent and severity of disease in patients with active, mild to moderate UC | $^{99m}$Tc-FDG-PET/CT colonography                                                  | Colonoscopy                                                                    | $^{99m}$Tc-FDG-PET scan does not increase CTe in detection of active disease |
| Ahmadi et al$^{31}$ | 2010        | Inflamm Bowel Dis        | 41       | To identify disease activity in patients with known or suspected active CD of the small intestine | $^{18F}$FDG-PET/CTe                                                             | Localized $^{18F}$FDG-PET/CTe                                               | $^{99m}$Tc-FDG-PET scan does not increase CTe in detection of active disease |
| Groshar et al$^{22}$ | 2010        | J Nucl Med               | 28       | To evaluate disease activity in patients with known or suspected active CD | $^{99m}$Tc-FDG-PET/CTe                                                          | Histology after surgery or after biopsy performed during endoscopy              | SUV$_{max}$ correlates well with CTe findings of active disease. It might be a reliable objective method for quantifying CD's activity |
| Shyn et al$^{33}$ | 2010        | J Nucl Med               | 13       | To detect active disease and assess severity of inflammation in patients with clinically suspected active CD | $^{99m}$Tc-FDG-PET/CTe                                                          | Endoscopy for distal ileum and colon, hydro-MRI for proximal ileum             | $^{99m}$Tc-FDG-PET added to CTe may improve the detection of active disease |
| Holtmann et al$^{21}$ | 2010        | Dig Dis Sci              | 43       | To detect bowel segments with active CD                                    | $^{18F}$FDG-PET                                                                 | Post-surgical histology                                                         | $^{99m}$Tc-FDG-PET diagnostic performance in the detection of bowel segments with active disease is high. Compared to $^{99m}$Tc-FDG-PET, hydro-MRI shows much lower sensitivity but higher specificity for all colon segments, higher sensitivity and the same specificity for terminal ileum and same performance for proximal ileum. Both methods seem to have high accuracy in strictures detection and characterization of their nature |
| Lenze et al$^{31}$ | 2012        | Inflamm Bowel Dis        | 30       | To detect CD strictures and differentiate inflammatory from fibrotic ones | $^{18F}$FDG-PET/CT enteroclysis, MR enteroclysis, transabdominal ultrasound        | Endoscopy + histology                                                          | All the three studied techniques have good strictures detection rates relating to the gold standard, but none of them can accurately differentiate strictures' nature. However, a combination of methods allows the detection of all strictures requiring surgery |
| Catalano et al$^{30}$ | 2016        | Radiology                | 19       | To differentiate fibrotic from inflammatory strictures in CD patients      | $^{18F}$FDG-PET/MR enterography                                                  | Post-surgical histology                                                       | $^{99m}$Tc-FDG-PET/MR enterography offers valid biomarkers for stricture evaluation |

SPECT: Single photon emission tomography; CD: Crohn's disease; UC: Ulcerative colitis; NA: Not available; $^{18F}$-FDG-PET: Positron emission tomography with $^{18F}$-Fluorodeoxyglucose; CT: Computed tomography; MRI: Magnetic resonance imaging; SUV: Standardized uptake value; CTe: CT esensitivity; pts: Patients.
The use of $^{99m}$Tc-HMPAO-WBC scan as initial screening modality to exclude IBD has been suggested, although controversial results have been reported. While a study showed that $^{99m}$Tc-HMPAO-WBC scintigraphy is more sensitive than upper gastrointestinal small bowel follow-through (SBFT)\cite{37}, other authors stated that $^{99m}$Tc-HMPAO-WBC scintigraphy should not be depended upon as a screening test for CD, since its performance compares unfavourably with each of the conventional investigative techniques\cite{38,39}.

Few data are available on other tracers. Peacock et al\cite{40} reported good results using $^{99m}$Tc- Stannous colloid WBC scintigraphy (88% sensitivity, 90% specificity) although agreement was poor for topographic localization of disease when compared to conventional imaging. However, due to a non-inferiority principle (results at least comparable to those of other WBC tracers) authors concluded that in children, $^{99m}$Tc-stannous colloid WBC scintigraphy should be preferred in view of lower cost, shorter preparation time, and smaller blood volumes required.

Bruno et al\cite{41} reported a higher sensitivity of immunoscintigraphy in CD than in UC (94% and 85%, respectively), although specificity was suboptimal in identifying clinical remission during follow-up. In fact, scintigraphy resulted positive during clinical remission in 73% of patients with CD and in 66.7% of patients with UC.

**Diagnosis:** PET: The paediatric literature studying the value of $^{18}$F-FDG-PET and $^{18}$F-FDG-PET/CT in IBD is limited, heterogeneous, and mostly restricted to retrospective studies.

One of the first article (published in 1999) was a retrospective study performed by Skehan et al\cite{18}. The authors included 25 young patients with suspected IBD who had undergone $^{18}$F-FDG-PET scan and colonoscopy with multiple biopsies, SBFT or both, which were used as a reference standard. $^{18}$F-FDG-PET uptake in the gut was considered pathological if greater than that of the vertebral spine. $^{18}$F-FDG-PET showed a per-patient sensitivity and specificity of 81% and 85%, respectively. On a segment-by-segment basis, PET correctly identified...
Table 5: Studies on molecular imaging in pediatric patients included in the present review

| Ref.        | Year | Pts (n) | Age (range) | Type of study | Clinical setting | Principal results                                                                 | Technique | Segments evaluated (n) | Criterion for positivity |
|-------------|------|---------|-------------|---------------|------------------|-------------------------------------------------------------------------------------|-----------|------------------------|---------------------------|
| Papo et al[36] | 1996 | 20      | 4-18        | Prospective   | IBD              | Sensitivity, specificity, and accuracy of LS were 93%, 88% and 91%, respectively     | Tc-HMPAO-WBC planar scintigraphy (30 min and 2 and 3 h) | 2-19                    | Scored relative to the normal bone marrow uptake (0, no uptake; 1 < bone marrow uptake; 2 = bone marrow uptake; and 3 > bone marrow uptake) |
| Charron _et al_[34] | 1998 | 178     | n.r.        | Retrospective | IBD              | Usefulness in distinguishing discontinuous from continuous colitis                  | Tc-HMPAO-WBC planar scintigraphy + SPECT (0.5-1 h, 2-4 h) | 2-15                    | Abnormal if activity was seen in the gut within the first hour. 0 = no labeling; 1 = less than bone marrow; 2 = greater than bone marrow, less than liver; and 3 = greater than or equal to liver |
| Cucchiara _et al_[33] | 1998 | 48      | 2-17        | Prospective   | IBD              | Significant difference in results of scintigraphy and endoscopy for the intensity of inflammation | Tc-HMPAO-WBC planar scintigraphy (dynamic + 30, 60, 120 and 180 min) | 178                    | 5-18                   | 9 |  |
| Del Rosario _et al_[33] | 1999 | 35      | 2-20        | Retrospective | IBD              | 83% sensitivity, which prompted more aggressive management in 75% of cases          | Tc-HMPAO-WBC planar scintigraphy (30 min + 2 h) | 4-19                    |  |
| Charron _et al_[33] | 1999 | 184     | n.r.        | Retrospective | IBD              | Sensitivity = 90%, specificity = 97%, overall accuracy = 95%                      | Tc-HMPAO-WBC planar scintigraphy + SPECT (0.5-3 h, 2-4 h, 5-6 h ≤ 24 h) | 2-16                    |  |
| Charron _et al_[34] | 2000 | 262     | n.r.        | Retrospective | IBD              | Useful as an initial screening modality to exclude IBD                            | Tc-HMPAO-WBC planar scintigraphy + SPECT (1-5 h, 1-2 h) | 4-19                    |  |
| Alberini _et al_[33] | 2001 | 28      | 2-15        | Retrospective | IBD              | Sensitivity and specificity were 75% and 92% for Tc-HMPAO-WBC                      | Tc-HMPAO-WBC planar scintigraphy + SPECT (0.5 h, 3 h, 1 p.i.) | 184                    | 64                     | Abdominal isotope uptake equal to or greater than that associated with the bone marrow was considered to indicate significant inflammation |
| Davison _et al_[34] | 2001 | 10      | n.r.        | Prospective   | CD               | Tc-HMPAO-WBC should not be relied upon as a screening test for Crohn’s disease    | Tc-HMPAO-WBC planar scintigraphy + SPECT (1 h, 1 h, 2-4 h) | 4-19                    |  |
| Bruno _et al_[34] | 2002 | 66      | 4-19        | Prospective   | IBD              | Sensitivity of immunoscintigraphy was 94% for CD and 85% for UC with a lower specificity | 99mTc-BW250/183 planar scintigraphy (4 h, 24 h, p.i.) | 10                    | 47                     |  |
| Grahnquist _et al_[34] | 2003 | 95      | 2-16        | Prospective   | IBD              | As a screening test for children with suspected IBD the calculated sensitivity was 75%, and the specificity was 82% | Tc-HMPAO-WBC planar scintigraphy (45 min + 3.5 h) | 184                    | 64                     |  |
| Peacock _et al_[34] | 2004 | 64      | 2-19        | Retrospective | IBD              | Tc-Stannous colloid LS had an 88% sensitivity, 90% specificity                   | Tc-Stannous colloid WBC planar + SPECT (1 h, 1 h) | 5-18                    |  |
| Chroustova _et al_[34] | 2009 | 40      | 5-18        | Monitoring    | IBD (17 = UC, 23 = CD) | Tc-HMPAO-WBC planar scintigraphy + SPECT (3.5 h, 2 h, 3 h) | Tc-HMPAO-WBC planar scintigraphy (50-60 min, 3 h, 2 h) | 10                    | 6                     | Graded 1-3 according to the uptake intensity. Grade 1 = a barely detectable abnormal uptake, grade 3 = an abnormal uptake at least as intense as that in the bone marrow and grade 2 was between these extremes. The extent of the abnormal uptake was subjectively classified as A (restricted to a single focus), C (diffuse, such as in pancolitis) or B (between these extremes) |
| Caobelli _et al_[34] | 2011 | 52      | 2-17        | Prospective   | IBD              | Sensitivity of 94%, specificity of 86%, and negative predictive value of 96% to diagnose IBD. During the follow-up, all relapses and remissions were correctly recognized | Tc-HMPAO-WBC planar scintigraphy (0.5 h, 3 h, 1 p.i.) |  |

SPECT: Single photon emission tomography; CD: Crohn’s disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease; WBC: White blood cell; LS: Leukocyte scintigraphy; pts: Patients.
the presence/absence of active disease in 60 of 79 (76%) bowel segments (sensitivity and specificity were 71% and 81%, respectively).

In 2005 Lemberg et al.\(^{[42]}\) published a prospective study including 65 children with newly diagnosed IBD (37/65 patients), with symptoms suggestive to recurrent disease (18/65 patients) or with recurrent abdominal pain (10/65 patients). \(^{18}\)F-FDG-PET scan results were compared with SBFT, pneumocolon and/or colonoscopy and demonstrated a per-patient sensitivity in UC \((n = 17)\), CD \((n = 38)\) and recurrent abdominal pain of 76%, 82% and 100%, respectively. The specificity of \(^{18}\)F-FDG-PET vs SBFT was 100% both for UC and CD, while it was 50% for CD and 81% for UC if compared to colonoscopy. The authors concluded that, although PET may not be able to replace conventional studies, it may be useful in case of difficult performance or failing of conventional studies. Additionally, Löffler et al.\(^{[43]}\) studied 23 children with suspected IBD in a retrospective study, comparing \(^{18}\)F-FDG-PET to endoscopy with biopsies and abdominal ultrasound. Inflammation was graded for each bowel segment on a 3-point scale, namely not inflamed, minimally inflamed and moderately-to-severely inflamed. \(^{18}\)F-FDG-PET scans were analysed semi-quantitatively calculating SUV for all bowel segments, normalized to that of the liver. A score \(> 3\) or a SUV\(_{\text{max}}\)/SUV\(_{\text{liver}}\) ratio \(> 1.2\) was considered positive for inflammation. \(^{18}\)F-FDG-PET showed higher sensitivity (98%) but lower specificity compared both to ultrasound (56% vs 92%) and to endoscopy (90% vs 75%). However, \(^{18}\)F-FDG-PET proved to be more reliable when assessing small bowel involvement (sensitivity = 100%; specificity = 86%; accuracy = 90%).

More recently, Däbritz et al.\(^{[44]}\) compared results of PET/CT to conventional diagnostic procedures on a segment-based analysis. An FDG uptake in the gut greater than that of the liver was considered pathological. Following these criteria, \(^{18}\)F-FDG-PET/CT showed per-patient sensitivity and specificity of 97% and 100%, respectively, and per-segment sensitivity and specificity of 82% and 97%, respectively (PPV 96%, NPV 88%, accuracy 91%). Berthold et al.\(^{[45]}\) retrospectively analysed 23 young symptomatic patients undergoing endoscopies (gastroscopy and colonoscopy) with biopsies, MRI and \(^{18}\)F-FDG-PET, eventually fused with CT, as part of the diagnostic workup. Positive PET findings were defined as a diffuse and clearly increased FDG uptake in the bowel. In this study, sensitivity and specificity of \(^{18}\)F-FDG-PET was 25% and 100% in the stomach and duodenum, 74% and 88% in the colon and 89% and 75% in the terminal ileum. Especially interesting was the diagnostic performance in assessing lesions involving terminal ileum, for which \(^{18}\)F-FDG-PET appears to be a reliable tool able for the non-invasive assessment of the presence and extent of the disease.

**Follow-up:** Only a few studies about paediatric patients have been published and are characterized by a smaller number of patients compared to those performed in adults and by the lack of an adequately long follow-up\(^{[46]}\). Chroustova et al.\(^{[47]}\) reported that \(^{99m}\)Tc-HMPAO-WBC scintigraphy may play an important role in the follow-up of patients with IBD if the findings are evaluated in conjunction with clinical symptoms and laboratory examinations, providing good information about the current stage of disease. Similar results were replicated by Papós et al.\(^{[48]}\), wherein the patient activity index scores (sum of the activity scores as measured in each bowel segment) were compared with laboratory parameters. The scintigraphic activity index showed an excellent correlation with several important activity markers in IBD, such as CRP, α2 globulin, iron, and erythrocyte sedimentation rate. Some impressive cases have been reported, in which \(^{99m}\)Tc-HMPAO-WBC scintigraphy could effectively trace the changing in disease activity over time in paediatrics (Figure 2).

However, despite some advantages of \(^{99m}\)Tc-HMPAO-WBC scintigraphy over conventional radiologic techniques in assessing acute inflammation activity, the post-operative relapse of Crohn disease and the inflammatory component of stenosis\(^{[49]}\), some disadvantages of this technique should be recognized. For example, the exclusive use of SPECT without CT combination cannot define anatomic changes in IBD such as stricture formation, fistula formation, or prestenotic dilation. These lesions are best demonstrated by contrast radiograph\(^{[50]}\). Moreover, these techniques require a blood sample, followed by reinjection\(^{[51]}\).

**PET represents a relatively novel technique for monitoring IBD\(^{[50]}\).** In contrast to the standard scintigraphy/SPECT, PET offers higher spatial and temporal resolution and is therefore more suitable for quantitative image analysis of physiological and pathologic processes\(^{[32]}\). However, the precise role of PET in the follow-up of paediatric patients diagnosed with IBD still remains to be defined for some clinical indication, such as differential diagnosis of fibrostenotic strictures from inflammatory strictures and as an alternative investigation after failure of conventional imaging\(^{[51]}\).

**New tracers and preclinical experiments**

Radiolabelled autologous leukocytes and \(^{18}\)F-FDG-PET represent two of the most widely adopted tracers to image IBD and other inflammatory diseases and have gained increasing acceptance for routine use. However, during the latest decade many efforts have been made in order to develop new radiopharmaceuticals able to detect inflammation and/or infection, such as labeled monoclonal antibodies, chemotactic peptides, interleukins and chemokines\(^{[52]}\) both for SPECT and PET imaging.

**SPECT tracers:** Neurath et al.\(^{[53]}\) enrolled 59 patients with CD in a prospective study, in order to assess disease activity by FDG-PET, hydro-MRI, and immunoscintigraphy with anti-nonspecific cross-reacting antigen 95 antigen-lyocyte antibodies. Twelve patients with irritable bowel syndrome and 20 patients with gut cancer but without gut inflammation served as controls. All three methods...
showed high specificity (89%) to detect inflamed areas in the terminal ileum and colon, although analyses by hydro-MRI and granulocyte antibody scan had strikingly lower sensitivities (40.9% and 66.7%) than FDG-PET (85.4%). Although hydro-MRI showed a higher sensitivity than immunoscintigraphy, still the diagnostic performance was suboptimal. Authors concluded that FDG-PET may provide improved diagnostic accuracy compared to the other two techniques.

Annovazzi et al \cite{55} compared \textsuperscript{99m}Tc-HMPAO-WBC scintigraphy to \textsuperscript{99m}Tc-IL2 scintigraphy in patients with CD. Both techniques provided high NPV (100% and 91%, respectively), unfortunately at expenses of a weak PPV (44% and 39%, respectively). However, only an unremarkable \textsuperscript{99m}Tc-IL2 scintigraphy was associated with longer disease free survival (log-rank test, $P = 0.013$). As such, the authors hypothesized a promising role for \textsuperscript{99m}Tc-IL2 scintigraphy is useful in selected patients with CD in clinical remission, who could benefit from preventive therapy to avoid disease relapse.

More recently, Van De Wiele et al \cite{56} investigated three different labelling methods for monocytes (\textsuperscript{99m}Tc-HMPAO, \textsuperscript{111}In-oxine and \textsuperscript{99m}Tc-colloids for SPECT studies or \textsuperscript{18}F-FDG for PET studies). Best results were yielded by \textsuperscript{99m}Tc-HMPAO. \textit{In vitro} labelled monocytes specifically accumulated in the intestinal activity foci. In 2015, Aarnotzen et al \cite{57} investigated the accuracy of \textsuperscript{99m}Tc-CXCL8 SPECT to detect and localize disease activity in a prospective series of patients with IBD. Radiolabeled CXCL8 (IL-8) targets the CXCL8 receptors mediating chemotaxis of immune cells to the site of inflammation. The overall sensitivity and specificity on a per-patient basis for the detection of active disease was 95% and 44% for \textsuperscript{99m}Tc-CXCL8 scan and 71% and 70% for endoscopy. Interestingly, the degree of \textsuperscript{99m}Tc-CXCL88 accumulation correlated to the degree of neutrophilic influx in affected mucosa.

PET tracers: New more specific PET radiopharmaceuticals for inflammation of the intestinal mucosa have been investigated. A gradual shift from large proteins with a nonspecific uptake mechanism to more specific targeting proteins could be observed in the latest years.

To date, neutrophil-mediated processes, characteristic for both inflammatory and infectious processes, can be targeted in situ by radiolabeled leukocytes, antibodies or its fragments and cytokines. \textsuperscript{68}Ga is one of the earliest positron-emitting radionuclides applied to clinical medicine, with a short physical half-life ($t_{1/2} = 68$ min), allowing favorable dosimetry with consequent lower dose delivered to the patients in case of repeated imaging. This constitutes a major advantage over the SPECT agent \textsuperscript{67}Ga\cite{58},

WBC labeled with \textsuperscript{18}F-FDG is a promising method for a non-invasive diagnosis and grading of intestinal inflammation. In both murine models and humans, \textsuperscript{18}F-FDG-WBC PET imaging demonstrated low tracer uptake in healthy gastrointestinal and urinary tracts, where the often unpredictable glucose metabolism often hinders the specificity of \textsuperscript{18}F-FDG-PET. In a study, intestinal foci of FDG-labeled WBCs were later confirmed to be inflammatory foci by histopathology. Moreover, the intensity of uptake well correlated with the degree of inflammation based on histopathologic criteria\cite{58}.

Preclinical experiments: Interleukins: Interleukins (e.g., IL-1, IL-2, IL-8) have recently been proposed as potential agents for imaging infection and inflammation\cite{59}.

In a rabbit model of acute colitis, Gratz et al \cite{59} investigated the diagnostic performance of \textsuperscript{99m}Tc-HYNIC-IL8 scintigraphy compared to \textsuperscript{99m}Tc-HMPAO-WBC scans. While both radiotracers detected colitis within 1 h after injection, \textsuperscript{99m}Tc-HYNIC-IL8 images were more accurate and the absolute uptake in the affected colon continuously increased until 4 h after injection, whereas no further increase was measured for \textsuperscript{99m}Tc-HMPAO-WBC beyond the first hour after the administration. The absolute uptake in the affected colon was significantly higher for \textsuperscript{99m}Tc-HYNIC-IL8 than for \textsuperscript{99m}Tc-HMPAO-WBC. The authors concluded that \textsuperscript{99m}Tc-HYNIC-IL8 scintigraphy, unlike \textsuperscript{99m}Tc-
HMPAO-WBC may provide a reliable estimation of the severity of IBD.

Preclinical experiments: (\(^{18}\)F)1-(2’-deoxy-2’-arabinofuranosyl) cytosine: The (\(^{18}\)F)1-(2’-deoxy-2’-arabinofuranosyl) cytosine (D-FAC) probe was developed as part of a broader effort to identify diverse molecular transport systems representing cellular biologic states\[^{59}\].

The biodistribution of D-FAC differs from that of FDG for a higher selectivity for immune organs such as the spleen, bone marrow, and thymus. In addition, D-FAC had strikingly higher uptake in the intestine in mouse models\[^{60}\]. While such increased uptake was thought to reflect the large amount of immune cells resident in the intestine mucosa, several lines of evidence revealed that intestinal D-FAC uptake is predominantly attributable to the intestinal epithelial cells. In fact, the distribution of the signal is strongly focalized in the duodenum, wherein the immune population is not significantly more expressed that in the remaining intestine\[^{60}\].

Uptake of \(^{18}\)F-D-FAC allows for a noninvasive assessment by PET. Increased uptake of D-FAC radiotracer reflects the activity of the epithelium and lymphocytes, providing a unique early marker of intestinal inflammation\[^{60}\].

Preclinical experiments: (\(^{18}\)F)DPA-714: (\(^{18}\)F)DPA-714, a radioligand of a translocator protein (TSPO), is another molecular probe developed for a non-invasive quantification of the inflammatory state of IBD in animal models\[^{61}\].

The TSPO is located on the outer membrane of the mitochondria and is overexpressed in the activated macrophages and microglia. This molecular event has been widely investigated in the pathologies of the central nervous system, representing a hallmark of brain inflammation. TSPO expression was recently described also in tissue samples of human colon suffering from IBD. Furthermore, its expression has been characterized in a rat model of IBD using autoradiography and immunohistochemistry\[^{62-64}\].

PET imaging of IBD was conducted using \(^{18}\)F-FDG and \(^{18}\)F-DPA-714 in two rat models\[^{61}\]. The first model was induced using dextran sodium sulfate (DSS), thus creating global inflammation in the colon, while the second one was induced by a rectal administration of trinitrobenzenesulfonic acid (TNBS), causing a local and acute inflammation.

The degree of inflammation was analyzed using PET imaging on days 7 and 8. In the first rat model, \(^{18}\)F-DPA-714 revealed significant differences between animals treated with DSS and controls (0.50% ± 0.17% ID/cc and 0.35% ± 0.15% ID/cc, respectively). Conversely, no differences could be seen using \(^{18}\)F-FDG. In the second model, the \(^{18}\)F-DPA-714 uptake significantly increased from 0.46% ± 0.23% ID/cc in the controls to 1.30% ± 0.62% ID/cc in the animals treated with TNBS. As such, a correlation between PET with increased TSPO expression at cellular level was fully demonstrated. The results of this study suggest that \(^{18}\)F-DPA-714 is suitable for studying inflammation in IBD models and could be a good molecular probe to define the degree and the localization of inflammation. Moreover, *in vivo* imaging using this TSPO ligand is potentially a powerful tool to stage and to follow inflammatory disease evolution and therapeutic efficiency at molecular level.

**DISCUSSION**

IBD represents a diagnostic and therapeutic challenge, not only at initial disease presentation, but also during suspected disease flares. Standard procedures like endoscopy and conventional radiologic studies are frequently required in order to assess the specific IBD subtype and evaluate disease extension and activity\[^{34}\]. Although endoscopy is an essential procedure for the diagnosis and follow-up of IBD, it is invasive and able to provide only a mucosal and not transmural assessment of the colon and the distal ileal segments. Furthermore, endoscopy is not always applicable during the active phase of IBD, especially in children\[^{48}\]. As such, there is the need for a noninvasive technique able to replace colonoscopy or conventional radiologic examinations in the follow-up of patients with IBD. This need is of particular importance in a paediatric population, as a highly variable response to therapy has been reported in these patients\[^{46}\]. As a consequence, a technique able to assess disease activity in paediatric patients plays a major role in yielding an IBD management. Since the simple clinical remission does not well correlate with the taming of the inflammatory process at the tissue level, an effective management of IBD represents a major challenge with the currently available diagnostic modalities.

Molecular imaging presents various advantages over colonoscopy. Firstly, it is minimally invasive and well tolerated by the patients, also by paediatric ones; second, patients can undergo the procedure also during the active state of disease, without any particular limitation or precaution; third, it should be noted that no intestinal preparation is needed; fourth, molecular imaging allows the evaluation of the colon and the terminal ileum. Presence of fibrosis does not impact the results of the examination. The investigation can be repeated over time, considering an adequate time interval. This latter aspect is of relevance especially during follow-up. Finally, molecular imaging has the potential to detect and characterize the anatomic location and the disease activity at diagnosis and on therapy.

All these advantages make molecular imaging particularly suitable in paediatric patients, either when an endoscopy has been refused by the young patient or if there is any specific contraindication\[^{34}\].

From the data of the literature, \(^{18}\)F-FDG-PET, eventually fused with CT, appears to have the best potential among molecular imaging techniques, since it provides the highest accuracy both in diagnosis and follow-up. In a recent meta-analysis by Treglia *et al*\[^{65}\] on 7 selected studies, including 219 patients with IBD, \(^{18}\)F-FDG-PET
(and PET/CT) showed pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio and diagnostic odd ratio of 85%, 87%, 6.19, 0.19 and 44.35, respectively. In their paper, the area under the ROC curve was 0.933. However, another meta-analysis by Zhang et al.\textsuperscript{21} including 20 prospective studies published between 1993 and 2013, did not report significant differences in sensitivity, specificity and diagnostic accuracy between \textsuperscript{18}F-FDG-PET and leukocyte scintigraphy. Following their results, the authors suggested that both techniques can be alternatively used for the diagnosis of IBD, depending on their local availability. Conversely, monoclonal anti-granulocyte antibody scintigraphy showed a significantly lower sensitivity, despite the higher specificity.

During follow-up, molecular imaging proved to effectively monitor therapy response. As a matter of fact, FDG represents the whole inflammatory burden of the gut, and an early post-therapy \textsuperscript{18}F-FDG-PET or PET/CT (within weeks from the start of the therapy) compared to a pre-therapy scan may allow for the early evaluation of therapy efficacy.

It seems that \textsuperscript{18}F-FDG-PET or PET/CT may have different indications, depending on the subtype of IBD. Spier et al.\textsuperscript{25} reported that \textsuperscript{18}F-FDG-PET has a good sensitivity in inflamed bowel segments in the patients with known IBD (range from 72.9% to 95.8%); while PET alone is at best suitable for patients with UC, PET/CT should be recommended in patients with CD, due to a better anatomical definition. It should also be noted that \textsuperscript{18}F-FDG-PET allows the visualization of the entire bowel wall in patients with known IBD. This ability is of particular importance in patients diagnosed with CD, since this condition is often characterized by a spread to the deeper layers of the bowel wall, where endoscopy fails to detect inflammatory lesions. Furthermore, PET can assess possible overlaps between irritable bowel syndrome and IBD prior to increasing or changing immunomodulation.

Despite these advantages, the use of FDG PET/CT in a clinical setting is still indeterminate. Indeed, there is no common consensus on the timing and on the number of the post-therapy scan and the predominance of studies involving small cohorts of patients represent a limit to support the use of this imaging technique in clinical practice. Many papers in literature underlined a suboptimal specificity for \textsuperscript{18}F-FDG-PET. Indeed, false positive cases due to physiologic uptake of the radiopharmaceutical in normal bowel can be often found in clinical practice. However, false positive findings can be effectively reduced with a proper distention of bowel segments through the administration of great amount of fluids\textsuperscript{1,2,4,7,20,21} or by specific patients preparations as reported by Franquet et al.\textsuperscript{22}.

In addition, a crucial question is the lack of a standardized method for quantifying accurately disease activity. Although many papers underlined the strategical role of semiquantitative parameters in PET imaging, still the huge heterogeneity of the published trials prevents to date to establish a robust assessment protocol.

It should also be mentioned that, to date, the widespread use of \textsuperscript{18}F-FDG-PET/CT (and to a lesser extent of \textsuperscript{99m}Tc-HMPAO-WBC scintigraphy) is hindered by relatively high costs and by relatively long waiting lists given its extensive use in oncology.

Finally, these procedures cause patient exposure to ionizing radiation (\textit{e.g.}, about 10 mSv for \textsuperscript{18}F-FDG-PET/CT, using the 50 mAs, 120 kV CT-protocol and an administered \textsuperscript{18}F-FDG activity of 3.7 MBq/kg). Several studies showed that risk of cancer is greater with earlier age of exposure. Therefore it is essential to avoid unneeded ionizing radiation exposure especially in paediatrics\textsuperscript{66}. It should be considered, however, that radiation exposure can be kept under acceptable limits by limiting the CT scan only to the abdomen-pelvis and/or using a 3D instead of a 2D scanner and a longer acquisition time with a lower administered \textsuperscript{18}F-FDG activity, if patient is able to remain still, or by using new reconstruction algorithms. The replacement of CT with MRI would significantly decrease the dose of radiations and improve diagnostic information on structural changes in bowel wall, despite a longer duration of the examination\textsuperscript{1,2,4,7,21,67}. Finally, considering an adequate time interval between serial examinations would limit the radioexposure into acceptable limits.

In conclusion, WBC scintigraphy and \textsuperscript{18}F-FDG-PET (alone or combined with CT or, in a next future, with MRI) represent a useful tool to detect active disease in IBD. However, the available data need to be validated in prospective multicenter studies on larger patient samples. Furthermore, even better diagnostic performance may be envisioned thanks to more specific and accurate radiotracers, which are however to date still far from a clinical validation in the clinical setting.
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