ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

Section Editor: Stephen B. Hanauer, MD

Current Use of Fecal Calprotectin in the Management of Patients With Inflammatory Bowel Disease

Marc Ferrante, MD, PhD
Associate Professor
Department of Gastroenterology and Hepatology
University Hospitals Leuven
KU Leuven
Leuven, Belgium

G&H What is fecal calprotectin?

MF Fecal calprotectin is a cytosolic component of neutrophils, which can be found in the intestinal bowel wall. When there is inflammation, specifically when there are erosions or ulcers, the neutrophils come into the lumen and burst open. Thus, the fecal calprotectin inside the neutrophils comes into the stool and can be measured. The measurement of this protein is becoming increasingly common in clinical practice. Because fecal calprotectin is regarded as a surrogate marker for endoscopic disease activity, it can give clinicians an idea of how sick a patient with inflammatory bowel disease (IBD) is without performing an endoscopy.

G&H What methods can currently be used to measure fecal calprotectin?

MF Several companies have developed techniques to test fecal calprotectin. Most of these involve classic enzyme-linked immunosorbent assays (ELISAs) or immunochromatography, for which stool samples are sent to laboratories for evaluation. However, more and more companies are also developing point-of-care tests, which allow clinicians to test fecal calprotectin during an office visit, and home-based tests, which enable patients to measure fecal calprotectin themselves at home.

G&H How reliable are the different ELISAs? Can they be used interchangeably?

MF Most of the ELISAs that are currently available have been validated extensively and are reliable. However, they are not identical, meaning that if a clinician starts using a specific fecal calprotectin test, it is best to stick to that particular test. The same stool sample might give different results with different tests. The same is true for point-of-care and home-based tests; if a clinician wants to follow fecal calprotectin in a patient, it is important that serial evaluations use the same test each time.

G&H What are the advantages and disadvantages of the different types of tests?

MF With an ELISA, several samples can be tested together. In addition, it does not require patients to handle stool samples themselves, which some patients do not like to do; I think there will always be some patients who prefer to bring a stool sample to a laboratory. On the other hand, there are some patients who do not like bringing in stool samples and would prefer to do the test themselves at their convenience. That is why I think home-based tests also have a role to play in fecal calprotectin testing.

G&H Have point-of-care and home-based tests become widely available?

MF Yes. More and more companies are bringing these tests onto the market. The tests have undergone validation and are reliable for use in clinical practice. Their uptake is quite good, although it mainly depends on

reimbursement. In Belgium, these types of tests are not reimbursed.

G&H How does fecal calprotectin compare to traditional inflammatory bowel markers such as C-reactive protein?

MF In the past, we only had access to classic blood testing for inflammatory markers. We mostly looked at C-reactive protein (CRP), which is a good inflammatory marker but it has the disadvantage of not always reflecting luminal disease. In addition, patients with ulcerative colitis only show increased CRP values in very severe conditions, while in Crohn's disease up to 40% of patients never have elevated CRP even in the case of severe luminal disease. Thus, only looking at CRP will produce some false-negative results, which does not happen as often with fecal calprotectin. However, fecal calprotectin is not 100% accurate, although it is a better surrogate marker for intestinal inflammation.

Nevertheless, CRP certainly still has its role. I would rather use CRP in combination with fecal calprotectin than not use CRP and only use fecal calprotectin. CRP shows more systemic inflammation, and there may be some patients with more ileal disease who have elevated CRP but no elevated fecal calprotectin.

G&H Currently, what is the role of fecal calprotectin in the diagnosis of IBD?

MF Several studies have looked into measuring fecal calprotectin for narrowing the indication for endoscopy to establish a diagnosis of IBD. As is well known, endoscopy is not the most pleasant experience for patients. If a patient has diarrhea and abnormal pain but no alarm symptoms, and the patient is not above age 50 years, the symptoms could suggest either IBD or irritable bowel syndrome. Measuring the patient's fecal calprotectin can be helpful when deciding whether endoscopic evaluation is needed. For example, if fecal calprotectin is normal, as are CRP and abdominal ultrasound, in a patient with nonspecific gastrointestinal symptoms, I do not think an endoscopy is necessary. It is quite useful to be able to determine whether an endoscopy is needed or not, especially in children, where the burden to undergo endoscopy is even higher. Of note, fecal calprotectin can be used by IBD specialists as well as by general practitioners.

G&H How can fecal calprotectin help assess disease activity?

MF As we know, patients do not always present with symptoms that reflect what is actually happening in their intestine. Sometimes patients have a lot of symptoms but an endoscopy does not reveal any inflammation, and sometimes patients do not have any symptoms but an endoscopy reveals severe inflammation. We also know that it is important to achieve endoscopic remission. Of course, an endoscopy cannot be performed every time a patient has an office visit. Thus, fecal calprotectin can be a good surrogate marker to help follow disease activity noninvasively. Measuring fecal calprotectin, in conjunction with using other diagnostic modalities, can determine whether it is worthwhile for a patient to undergo endoscopy or change their treatment.

G&H Can fecal calprotectin also help assess response to therapy?

MF Yes, it can be helpful to follow fecal calprotectin when a patient starts a therapy in order to see whether the patient is responding or not. At the beginning, the patient's fecal calprotectin will mostly be elevated, and the clinician can take measurements during treatment to see whether it is indeed efficacious, reflected by a decrease in fecal calprotectin. When assessing response, it is important to look not just at one value but at serial measurements of fecal calprotectin because there is always some variability.

In addition, I do not rely on a single measurement to implement significant treatment adjustments because there may be other reasons for changes in fecal calprotectin besides test variability; for example, the patient might have nonsteroidal anti-inflammatory drug–induced enteropathy. Currently, I only switch from one therapy to another when I see with my own eyes that there is active inflammation (ie, when I perform an endoscopy or magnetic resonance enterography). Fecal calprotectin measurement helps guide in whom I perform an endoscopy, but the measurement itself is not sufficient, at least right now, for me to change treatment.

G&H Has there been any research looking at whether fecal calprotectin can help predict disease relapse?

MF Indeed, there have been some data suggesting that routine monitoring of fecal calprotectin when patients discontinued treatment can predict relapse. This monitoring can also allow clinicians to act rapidly in order to prevent the relapse from occurring. However, testing probably needs to be done at least every 2 or 3 months, and it is not always easy to convince a patient who is asymptomatic to undergo such testing.

G&H Is there a role for fecal calprotectin in the prediction of mucosal healing?

MF There is quite a good correlation between endoscopic disease activity and fecal calprotectin, so it might be expected that a patient who has achieved endoscopic remission also has a fecal calprotectin that has normalized. However, it should be pointed out that, as for all tests, there are always some false-negative and -positive results. Fecal calprotectin is certainly not a 100% accurate marker.

G&H What is the current role for fecal calprotectin in the prediction of postoperative disease recurrence?

MF In most hospitals, endoscopies are performed 6 to 12 months after an ileocolonic resection with ileocolonic anastomosis. Some studies have suggested that the need for these endoscopies can be based on the patient's fecal calprotectin, as there seems to be a correlation between recurrence of postoperative Crohn's disease and fecal calprotectin. However, as mentioned above, this marker is not 100% accurate, so I do not rely only on fecal calprotectin in the postoperative setting. I always perform an endoscopy in addition to measuring fecal calprotectin and then follow the patient's fecal calprotectin as a surrogate marker for what I saw during the endoscopy.

G&H Are there accepted cutoffs for fecal calprotectin use in IBD patients?

MF The cutoff depends on the type of test being used. Traditionally, a cutoff of 50 µg/g is used to diagnose IBD, and if a patient is known to have IBD, the cutoff for relevant endoscopic disease activity is usually 250 µg/g. As previously mentioned, it is important to use not just one measurement, certainly not in a patient who is asymptomatic, unless his or her fecal calprotectin is extremely high.

G&H What are the main limitations of using fecal calprotectin?

MF One limitation is that it seems to correlate mainly with colonic disease, and less with ileal disease. This should certainly be taken into consideration when discussing the accuracy of fecal calprotectin measurement in patients with Crohn's ileitis. On rare occasions, the measurement may give the impression that a patient is fine when, in fact, there is ongoing inflammation.

In addition, as previously discussed, there is some variability in fecal calprotectin testing, so serial measurement is essential. There may also be difficulties in interpretation depending on the consistency of the stools. The timing of the fecal sample is also important; it is ideal to use a fresh morning stool sample for analysis.

Other limitations involve the participation of the patients. Not all patients are willing to bring a stool sample to the clinic or test it themselves at home. Thus, there is still a need to look into other biomarkers that are easier for patients to handle.

G&H What other research is needed in this area?

MF We should look for even better biomarkers, not only for patients with IBD and individuals suspected of having IBD, but perhaps also for healthy relatives. The tests evaluating biomarkers should be easily accessible and patient-friendly and should accurately guide further diagnostic or therapeutic decisions.

Dr Ferrante has received research grants from Amgen, Biogen, Janssen, Pfizer, and Takeda; has consulted for AbbVie, Boehringer Ingelheim, Janssen, MSD, Pfizer, Sandoz, Takeda, and Thermo Fisher; and has received speaker fees from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Falk, Ferring, Janssen, Lamepro, MSD, Mylan, Pfizer, Sandoz, and Takeda.

Suggested Reading

D'Haens G, Ferrante M, Vermeire S, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm Bowel Dis*. 2012;18(12):2218-2224.

Lehmann FS, Burri E, Beglinger C. The role and utility of faecal markers in inflammatory bowel disease. *Therap Adv Gastroenterol*. 2015;8(1):23-36.

Walsham NE, Sherwood RA. Fecal calprotectin in inflammatory bowel disease. *Clin Exp Gastroenterol*. 2016;9:21-29.

Zittan E, Kelly OB, Gralnek IM, Silverberg MS, Steinhart AH. Fecal calprotectin correlates with active colonic inflammatory bowel disease but not with small intestinal Crohn's disease activity. *JGH Open*. 2018;2(5):201-206.