ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Fecal Biomarkers for the Diagnosis and Management of Inflammatory Bowel Disease

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G&H Why have researchers tried to identify fecal biomarkers for inflammatory bowel disease?

GVA The gold standard for diagnosing and following patients with inflammatory bowel disease (IBD) has been endoscopy, which is quite invasive. While a flexible sigmoidoscopy is less invasive, a full colonoscopy requires bowel preparation and sedation, so patients do not like undergoing this procedure. Colonoscopy is also very time-consuming and very expensive.

The second reason for studying biomarkers is that clinical scores for ulcerative colitis (UC) and Crohn's disease (CD) are subjective, both because patients give subjective assessments of their symptoms and because clinicians are subjective in their assessments of patients. This subjectivity has created several problems, both in clinical trials—where we see high placebo effects—and in clinical practice—where we observe symptoms but cannot be sure that these symptoms are due to inflammation.

Traditionally, when we talk about biomarkers for IBD, we mean serologic markers such as C-reactive protein (CRP), which has been the paramount biomarker for measuring inflammation in IBD for the last 10–15 years. However, there are 2 caveats with CRP testing: First, CRP is nonspecific; it measures inflammation, but it does not tell us where that inflammation is occurring—it could be in the bowel, or it could be somewhere else in the body. Second, CRP is a good marker for CD, but it is not a very good marker for UC, except in patients with severe disease who are in the hospital. In looking for better biomarkers, we hope to find a test that is more specific for bowel inflammation, as well as being applicable to both UC and CD.

G&H What are the advantages and disadvantages of fecal biomarkers?

GVA Theoretically, the big advantage of fecal biomarker testing is that these tests measure proteins originating in the intestinal mucosa, which means that they should reflect purely intestinal inflammation. This specificity for the bowel is the main advantage of fecal biomarkers. Analyzing a stool sample is also less invasive than performing a full colonoscopy, and being able to eliminate the need for colonoscopy has become very important in some settings, especially with pediatric patients.

The disadvantage of fecal biomarkers is that they are not specific for IBD. Although fecal biomarkers are specific for intestinal inflammation or intestinal lesions, we do not know whether this inflammation is associated with IBD per se. For example, a patient who is taking nonsteroidal anti-inflammatory drugs (NSAIDs) will also have increases in fecal inflammatory markers like calprotectin or lactoferrin. Therefore, a negative fecal biomarker test is predictive of having no lesions in the bowel, but a positive fecal biomarker test is less specific or indicative. A positive fecal biomarker test tells you that the patient has inflammation or lesions somewhere in the bowel, but not whether these findings are related to IBD. Thus, fecal biomarker testing has a very high negative predictive value, but its positive predictive value is lower.

G&H How do fecal biomarkers compare with serum biomarkers for facilitating diagnosis, predicting treatment response, and evaluating response to treatment?

GVA From a diagnostic standpoint, there is a nice correlation between the presence of endoscopic lesions and elevations in calprotectin or lactoferrin levels. There is less of a correlation between fecal markers and CRP levels or clinical indices, but significant correlations are still observed.

In terms of monitoring patients after diagnosis, we have emerging data from several groups showing that improvements in fecal biomarkers nicely coincide with improvements in endoscopy among patients responding to therapy. Much of that data has been gathered from just a few sites—such as Helsinki, Finland—but some data have come from other sites. Overall, fecal biomarkers seem to be very good indicators of treatment response, specifically in UC, but also in patients with CD.

G&H What is the specific role of calprotectin and lactoferrin in IBD?

GVA Calprotectin and lactoferrin are both proteins that are derived from neutrophils. Therefore, whenever there are neutrophils in the mucosa, they will secrete these proteins, both of which are highly stable in feces. The fecal environment is an aggressive environment for most proteins—there are many proteases due to the bacteria in feces—but calprotectin and lactoferrin are resistant to this enzymatic breakdown, so it is possible to measure these proteins in a fecal sample. In addition, samples can be stored for several days and shipped at an ambient temperature. At this time, fecal calprotectin is more frequently used in clinical trials and clinical practice because tests for this biomarker have been more extensively validated, but lactoferrin has also been shown to be a very good marker for intestinal inflammation, specifically for colonic inflammation.

G&H Are there any other fecal biomarkers that are commonly measured in IBD?

GVA Calprotectin and lactoferrin are the most reliable fecal biomarkers currently measured in clinical practice. There are other proteins that are derived from neutrophils, but I do not know if testing for these proteins will be introduced in the clinic in the near future.

G&H How well do calprotectin and lactoferrin levels correlate with disease activity?

GVA There is a good correlation between fecal biomarkers and disease activity, both in children and adults: levels of these biomarkers are elevated in patients with active IBD but are much less elevated in quiescent IBD. There has been much attention to the correlation between fecal biomarkers and disease activity in children, in particular, as many clinicians would like to use fecal biomarker testing to avoid the need for endoscopies in these patients. For example, if a clinician suspected IBD in a child but fecal biomarkers were normal, then the clinician might be able to avoid performing an endoscopy, which is quite an interesting challenge in a 4-year-old child. There is a very good correlation between the absence of lactoferrin and/or calprotectin and absence of intestinal and colonic inflammation, which can allow IBD to be ruled out in some cases.

G&H Why are calprotectin and lactoferrin levels elevated in active IBD?

GVA Calprotectin and lactoferrin levels are elevated in IBD because they are secreted by neutrophils. Neutrophils are nonspecific inflammatory cells, but they are recruited to any site of inflammation—specifically the bowel, in the case of IBD. When bowel mucosa is shed into the feces or when a patient has ulcers, these neutrophils break down and appear in the feces. Because calprotectin and lactoferrin make up an extremely high proportion of the cytosolic proteins of these cells, these proteins will appear in the stools, and they are very stable in this environment. Thus, measurement of these biomarkers provides a reliable gauge for the degree of inflammation in the bowel. However, they are not specific for IBD, because any type of inflammation will give rise to neutrophils in the mucosa, whether it is due to acute infection or pharmacotherapy (as with NSAIDs).

G&H What data are available regarding the utility of these biomarkers in patient management?

GVA Fecal biomarkers have been studied both as a diagnostic tool and as a tool for monitoring response to therapy, and data are available to support both uses. However, I believe the latter application is going to be the prime use of fecal biomarkers. Studies have shown that these biomarkers can predict disease relapse or announce a flare, so careful monitoring of these markers could allow clinicians to instigate earlier treatment or further testing, as appropriate.

G&H Is fecal biomarker testing currently available in most clinical settings?

GVA Availability of these tests varies among different countries. In quite a few regions in Europe—specifically Scandinavia, Switzerland, and the United Kingdom—doctors are increasingly using fecal biomarker testing, and it is becoming more widely available. However, it is not yet reimbursed in every country. In the United States, fecal biomarker testing is available, but not all centers are using it.

G&H Do you expect that fecal biomarker testing is going to become more common?

GVA Yes. I think we will also see new applications for these tests. For example, there is a very clever program being conducted in Denmark in which fecal biomarker testing is being used for monitoring of disease activity and patient self-management. In this program, patients perform their own calprotectin test at home, take a picture of the test result with their cell phone, and send the image to the doctor's computer system. Then the doctor can decide whether the patient needs to intensify therapy or not.

G&H In which patients are measurements of fecal biomarkers most useful?

GVA Children are a prime group for fecal biomarker testing; the main benefit in this population is that biomarker testing can help clinicians avoid invasive testing. I should note that most pediatric gastroenterologists use full sedation and anesthesia when performing a full colonoscopy, which makes it quite invasive for pediatric patients.

Other patients who can benefit from fecal biomarker testing are those who might be having a subclinical flare and patients in whom the clinician has doubts about the origin of patients' symptoms. For example, a patient with a recurrence of symptoms may be having an IBD flare, but these symptoms could also be due to a functional bowel syndrome provoked by the patient's previous inflammation. In this case, performing a calprotectin test can make a difference: While a positive test result will probably prompt further evaluation, a negative test would imply that there is no inflammation, in which case additional anti-inflammatory drugs could be avoided.

G&H In which patients are biomarker tests less useful?

GVA Fecal biomarker testing is less necessary in patients who can be easily assessed by endoscopy and/or at clinical sites where an endoscopist is readily available to perform flexible sigmoidoscopy. In addition, we do not know for sure how well these biomarkers behave in patients with pure ileal or upper gastrointestinal CD or those with an ileoanal pouch, so biomarker testing may not be helpful in these cases. Finally, fecal biomarker testing is not very informative in patients who are taking NSAIDs. For example, if a patient with spondyloarthropathy is taking NSAIDs, the drug would likely cause a false-positive result, in which case the clinician would not gain any information about whether the patient also has IBD.

G&H Does the utility of these tests differ between children and adults? Do you have to interpret fecal biomarker tests differently in children?

GVA No, the testing is equally effective in both children and adults. In both populations, however, there is the problem of which threshold should be used to diagnose IBD. The chosen cutoff could be test-dependent and may differ between children and adults. In general, however, fecal biomarker testing is comparable in both populations.

G&H What further research is needed regarding the use of fecal biomarkers?

GVA We need more data showing how these tests could be used to predict a subclinical flare so that we can intervene earlier. We also need data showing that these tests are reliable for measuring treatment effects and that they can allow clinicians to safely avoid endoscopy. Finally, we need more harmonization of the different assays that are now available. Fecal biomarker testing is an evolving field with a lot of promise, but we still need more validation.

Suggested Reading

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