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VIEWPOINT

Concept for a rapid point-of-care calprotectin diagnostic test for diagnosis and disease activity monitoring in patients with inflammatory bowel disease: Expert clinical opinion

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1. Introduction

Inflammatory bowel diseases (IBD), such as ulcerative colitis (UC) and Crohn's disease (CD) are organic inflammatory diseases, caused by chronic mucosal inflammation of the intestine. They are typically characterized by variable disease activity, often with repeated periods of intermittent disease activity and remission. Irritable bowel syndrome (IBS) is a non-inflammatory functional disorder and, by definition, presumes the absence of organic disease.[1] As the presenting manifestations of IBD and IBS are similar and can include diarrhea, abdominal pain and bloating, obtaining a clinical diagnosis can be difficult, and further invasive diagnostic procedures may be required in order to obtain a confirmed diagnosis.[2,3]

Treatment strategies based on presenting clinical manifestations have failed to modify the course of IBD.[4,5] Indeed clinical disease activity indices are non-specific and do not correlate with endoscopic activity.[2,6,7]

Mucosal healing has emerged as a new therapeutic goal in clinical practice and is regarded as a major endpoint definition for remission of IBD in clinical trials, due to its association with improved outcomes in IBD, including reduced relapse and hospitalization rates, and reduced need for surgery.[8] C-reactive protein (CRP) is a non-specific marker that reflects systemic inflammation and is useful for the detection of complications (such as abscesses) or extraintestinal manifestations.[9–14] However, it is not an accurate marker of mucosal healing.[15]

There is currently an unmet medical need for a suitable non-invasive biomarker of mucosal inflammation, arising primarily because of the inherent problems associated with endoscopy, which is an invasive and expensive procedure.

Although cross-sectional imaging methods such as MRI,[16,17] CT, and ultrasound are used for assessing disease activity in patients with UC and CD, there is still room for the use of fecal markers to evaluate mucosal lesions in clinical practice. In addition, a non-invasive test might be used to anticipate flares in IBD activity, which would allow for pre-emptive escalation of treatment. The ideal marker should be specific and sensitive, inexpensive, yield rapid results, which could be available during the patient visit, and have a high negative predictive value.

This article reports the outcomes of a recent meeting of a panel of gastroenterologists with expertise in IBS/IBD and fecal biomarkers to discuss the development of a rapid point-of-care semi-quantitative test to enable discrimination of IBD from IBS, and subsequent disease activity monitoring in patients with IBD.

2. Materials and methods

In April 2012, 11 gastroenterologists with expertise in IBS/IBD and special interest in fecal biomarkers met in Zürich, Switzerland to discuss the potential for development of a rapid point-of-care, semi-quantitative test. The meeting focused on the following main questions:

1. What is the rationale for choosing fecal calprotectin as the most suitable IBD biomarker for the test, compared with other fecal markers such as lactoferrin or M2-pyruvate kinase (M2-PK)?
2. What would be the agreed number and cut-off calprotectin level values for various clinical settings?
3. Would it be useful to have different cut-off levels for UC and CD?
4. Could patients with IBD tailor their treatment to allow earlier escalation of their treatments to prevent a relapse of their disease or, alternatively, reduce their treatment if their disease was known to be in remission as indicated by the results of their fecal marker rapid point-of-care test?

Finally, the expert panel discussed the next steps in terms of a clinical study concept to validate agreed consensus calprotectin cut-off levels.

3. Results

A non-invasive, point-of-care diagnostic test would be of interest in order to reduce the number of invasive and expensive endoscopies, which are undertaken to diagnose suspected IBD, differentiate UC from CD, and determine the extent and severity of mucosal inflammation.

3.1. Candidate markers for a rapid point-of-care diagnostic test

Inflammation of the intestine during the acute-phase IBD is associated with migration of leukocytes to the gut, resulting in the production of a large number of inflammatory proteins which can be measured in the feces. As a result, several leukocyte products and serum proteins have been evaluated for use as fecal markers, which can be used to indicate the presence and severity of intestinal inflammation.[10,18] Possible fecal markers for IBD include lactoferrin, M2-PK, S100A12, calprotectin and polymorphonuclear neutrophil elastase (PMN-elastase). The characteristics of these IBD markers are summarized in Table 1.

Lactoferrin is an iron-binding glycoprotein found in neutrophil granulocytes; its levels in feces have been shown to increase quickly following inflammation of the intestine.[18] Studies have reported that lactoferrin is a sensitive marker of IBD activity[19–21]; however, it is not as widely studied as calprotectin. Walker et al. reported promising results from a study of 148 children and young adults with IBD (141 with IBD and 7 with IBS, plus 22 healthy controls) in which elevated lactoferrin levels were used to identify patients at greater risk of disease relapse.[22]

M2-PK is an enzyme involved in glycolysis that is present in rapidly dividing cells and has been previously used as a marker of gastrointestinal cancers.[23] However, its role in gastrointestinal inflammation is unknown. A study by Chung-Faye et al. reported elevated concentrations of M2-PK in patients with IBD compared with those patients with IBS. However, it has yet to be shown if M2-PK can be used as a potential marker for predicting relapses in asymptomatic patients with IBD.[24]

PMN-elastase is a serine proteinase that is secreted by neutrophils and macrophages during inflammation. The concentrations of PMN-elastase in feces correlate with intestinal inflammation. A study by Schröder et al. identified the use of PMN-elastase as a possible tool for the differential diagnosis of IBS; however, its overall diagnostic accuracy (sensitivity for identifying inflammation and specificity for excluding