Austin Journal of Gastroenterology

Open Access

Austin Publishing Group

Review Article

Bio-Markers of Inflammatory Bowel Disease: Past, Present, and Future

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Received: March 07, 2017; **Accepted:** April 25, 2017; **Published:** May 09, 2017

Abstract

Ulcerative colitis (UC) and Crohn's disease (CD) exemplify the two main arms of the spectrum of an idiopathic chronic disease known as inflammatory bowel disease (IBD). To date, this disease remained a puzzling dilemma in many aspects; including difficulties in its etiology/pathogenesis, diagnosis, severity assessment, treatment and outcomes/complications. Physicians usually get the diagnosis of IBD through a combination of clinical features, laboratory tests, radiology, as well as the invasive technique of endoscopy/biopsy. In spite of these efforts, the definite diagnosis can't be established in a significant cohort of cases. This paved the way to searching for laboratory biomarkers that are noninvasive, reproducible, rapid and relatively cheap than other modalities. Unfortunately, we're still far from these ideal biomarkers. Some biomarkers are already being used in daily practice including C-reactive protein (CRP) and fecal calprotectin while others are still in need for confirmation before being applied in clinical practice. In this review article, the authors are going to discuss the past, present, and future utility of biomarkers in IBD. This article aims at highlighting the uses and limitations of all possible current and novel biomarkers in every aspect of the disease from predisposition to prognosis.

Keywords: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Biomarkers; ANCA; ASCA; calprotectin; Lactoferrin; Neopterin; ESR; C-reactive protein; Lipocalin-2; Infliximab

Abbreviations

IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn's Disease; ANCAs: Antineutrophil Cytoplasmic Antibodies; FC: Fecal Calprotectin; ASCAs: Anti-Saccharomyces Cerevisiae Antibodies; FL: Fecal Lactoferrin; FN: Fecal Neopterin; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; RDW: Red Blood Cell Distribution Width; ADA: Adenosine Deaminase; LCN2: Lipocalin-2; sST2: Serum Soluble ST2; eNO: Exhaled Nitric Oxide; ATIs: Antibodies to Infliximab; TPMT: Thiopurine Methyltransferase; 6TGN: 6-Thioguanine Nucleotide

Introduction

Biomarkers of etiology/pathogenesis

Background: Multiple genes for IBD had been discovered, but only three had been claimed for a direct role in the etiology and pathogenesis of IBD.

NOD2: Sequencing for NOD2 variants appears of substantial importance in CD patients for predicting ileal location, stenotic lesions and complicated course [1,2]. This seems relatively more important among Caucasians particularly Turkish and Iranian patients with CD [3,4].

IL-23 receptor gene (IL23R): IL23R is a CD susceptibility gene which is expressed as two opposing types of variants in different populations; IBD risk-increasing and IBD risk-decreasing variants [5-7].

This variance could also modify treatment plans. As an example, homozygous carriers of IBD risk-increasing variants are more likely to respond to anti-TNF than homozygous carriers of IBD risk-decreasing variants [8].

Autophagy Genes: CD risk is increased through autophagy-regulating genes including autophagy 16-like 1 (*ATG16L1*), immunity-related guanosine triphosphatase M (*IRGM*), and leucine-rich repeat kinase 2 (*LRRK2*) genes [9,10]. This association, however, is race-dependent [11-13]. So future researches are needed to map it.

To summarize, biomarkers depending on gene sequencing seems associated with predisposition to CD rather than UC with none of them being currently in use awaiting confirmation by future research.

Biomarkers of diagnosis

Background: The rationale for diagnostic biomarkers relies upon the immune mechanism of chronic inflammation in IBD. Their use is of particular importance when diagnosing and/or differentiating UC and CD by the combination of clinical, endoscopic, and histopathologic features seems confusing. The two main currently used immune-related biomarkers are pANCA and ASCA while the utility of many other immune markers in the diagnosis and differential diagnosis of IBD needs future research to validate their practical use including anti-OmpC, ALCAs, ACCAs, AMCAs, antiL, and anti-C and pancreatic autoantibodies (PAB) [14-17].

Fecal calprotectin (FC): Fecal calprotectin was first described in 1980 by Fagerhol, et al. [18]. It is a protein released by the white blood cells involved in inflammation of the bowel. In that way, a high level correlates with bowel inflammation. After binding to calcium,

Citation: Bahgat MH and El-Etreby SA. Bio-Markers of Inflammatory Bowel Disease: Past, Present, and Future. Austin J Gastroenterol. 2017; 4(2): 1082.

it becomes a stable compound in the intestines. It can be measured by laboratory tests, including the more recent point-of-care testing (POCT) [19]. This interesting characteristic of its stable distribution in feces reflects the need to examine only one sample of stool [20].

A systematic review by Waugh, et al. concluded that FC can be used to differentiate between IBD and IBS at a cut-off level of 50 μg/g in both adults and children with sensitivities of 83-100% and specificities of 60-100% in adults and sensitivities of 95-100% and specificities of 44-93% in children [19].

Anti-neutrophil cytoplasmic antibodies (ANCAs): In 1990, Rump, et al. suggested the possible use of a new type of perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) in active UC but not CD [21]. The utility of these antibodies in association with ASCA in diagnosing difficult cases of indeterminate colitis (IC) was illustrated by Joossens, et al. when they determined that ASCA+/pANCA- status predicts CD in 80% of patients with IC while ASCA-/pANCA+ status predicts UC in 63.6% of patients with IC [22]. However, it should be noted also that pANCA might be positive in rheumatoid arthritis and even in nearly one third of healthy individuals [14,23].

Anti-Saccharomyces cerevisiae Antibodies (ASCAs): In 1988, a study by Main, et al. reported antibody to Saccharomyces cerevisiae (bakers' yeast); a common dietary antigen, in patients with IBD and in controls. They found a considerable difference in titers of ASCAs between patients with CD and those with UC which was different from previous reports that suggested a generalized increase in antibody to food antigens in people with IBD which may reflect increased exposure to antigens owing to an inflamed or damaged bowel wall, i.e., secondary to the primary disease process. In their study, the response to S cerevisiae seemed to be quite specific to CD which can't be explained as a secondary phenomenon. Furthermore, the difference between the two diseases cannot be accounted for on an anatomical basis, as increased titers of ASCAs were not confined to patients with CD of the small bowel. ASCAs are antibodies against mannan in cell wall of S. cerevisiae [24] with high specificity of 90-100% in CD but relatively low sensitivity of 31%-45% [25]. Finally, it should be noted that ASCA and atypical P-ANCA markers are not useful for IBD screening. A study by Mokhtarifar, et al. suggested that while atypical P-ANCA may be useful in differentiating UC from CD, ASCA is of limited value for screening and differentiating UC from CD [26].

Biomarkers of disease activity

Background: Various markers of activity and inflammation have been introduced with a concern about their individual sensitivity and specificity. Using a combination of these markers may be more useful for predicting disease activity and confirming inflammation. Some of these markers are already in current use; others are still emerging.

Markers in current use:

Fecal calprotectin (FC): As discussed earlier, FC reflects the process of inflammation, so it is a reasonable marker for assessment of IBD activity [27]. One meta-analysis confirmed that fecal calprotectin is better than the other currently used markers particularly CRP, ESR, ASCA, and pANCA [28]. Another meta-analysis showed that fecal calprotectin can reduce endoscopy rate by 67%, while delaying treatment of patients by 6% [29]. Another important feature is the differential level of FC according to the site of IBD where it is found to be significantly higher in active colonic rather than ileal CD [30]; and in left-sided/distal UC than ulcerative pancolitis [31]. Finally, FC could be used as a marker for treatment assessment [32] as it decreases considerably after anti-TNF therapy, and it correlates with CD endoscopic index of severity (CDEIS) [33] as well as endoscopic mucosal healing [34]. Koulaouzidis, et al. suggested that FC can direct the use of special costly investigations as capsule endoscopy which can be declined if FC level is less than 100 μg/g [35].

Fecal Lactoferrin (FL): Lactoferrin is an iron-binding protein component of neutrophils that covers most of the mucosal surface and is activated in acute inflammation [36] suggesting its use in inflammation of intestine. FL increases significantly with bowel infiltration by neutrophils and is stable in feces for 5 days [37]. The diagnostic accuracy of lactoferrin for IBD could reach up to 80% when compared with IBS, which is rather similar to FC and better than CRP [38]. FL is also associated with disease activity [39].

Fecal Neopterin (FN): Neopterin is a product of human monocytes and macrophages stimulated by γ-interferon. Both fecal calprotectin and fecal neopterin concentrations are correlated with endoscopic scores in UC better than in CD. Using cutoffs of 250 μg/g for fecal calprotectin and 200 pmol/g for fecal neopterin, both fecal markers have similar overall accuracy to predict endoscopic activity in patients with CD (74%) and a relatively higher accuracy in patients with UC (88% and 90%, respectively) [40].

C-reactive protein (CRP): CRP is an acute phase protein secreted by hepatocytes in healthy individuals at a very low level of <1 mg/L. Being one of the most important protein in acute inflammation [41], it sharply increases to very high levels that may reach 350-400 mg/L with acute inflammation while lesser levels of elevation in the range of 10-40 mg/L may indicate chronic inflammation as IBD. However, for unknown mechanism, it correlates significantly with CD but not UC [42,43] while high-sensitivity C-reactive protein (hs-CRP) and β2-microglublin correlate with histology scores of UC [44]. To summarize, CRP can be falsely low despite active mucosal inflammation while it is more reliable in transmural inflammation [45].

Erythrocyte Sedimentation Rate (ESR): Like CRP, ESR is a measure of systemic inflammation and thus no-specific to IBD. Unlike CRP, ESR levels peak later and decrease at a slower rate. So, ESR is better in monitoring disease activity and response to treatment after the first 24h of onset whilst CRP may be more useful in the first 24h [46]. However, the longer half-life of ESR as well as its interference with other factors makes ESR less useful in clinical practice compared with CRP [47].

Platelets count and mean volume: Increase in platelets counts in IBD might represent the hypercoagulable state of IBD [48-50] particularly the reticulated platelet levels which increase significantly in UC [51]. Mean platelet volume (MPV) points toward average size of platelet reflecting the rate of platelet stimulation and production. One study [52] found that MPV decreased significantly in active IBD, and it was negatively correlated with CRP and ESR while another study [53] failed to confirm this relationship.

Red blood cell distribution width (RDW): RDW reflects the

size and variability of red blood cells in peripheral circulation [54]. A study involving 221 IBD (120 UC and 101 CD) found that RDW is better than CRP and ESR in predicting CD activity in absence of anemia [55].

Emerging/novel markers:

Fecal S100A12: S100A12 is a novel biomarker which is similar to calprotectin in its calcium-binding properties [56] that increases cytokine release [57]. Although it is also detectable in serum, the fecal assay is more sensitive and specific for IBD [58].

Adenosine Deaminase (ADA): ADA may be a new biomarker for CD activity [59].

Lipopolysaccharide-binding protein (LBP) and soluble CD14 (sCD14): In IBD, enhanced inflammatory activity in the gut is thought to increase the risk of bacterial translocation and endotoxemia. Lakatos, et al. investigated the association between serum level of LBP and sCD14 with clinical disease activity and they suggested both as markers of disease activity in CD with accuracy similar to that of hs-CRP [60].

Lectin-based immunoassay for aberrant IgG Glycosylation: Shinzaki, et al. [61] found that agalactosyl fraction among fucosylated IgG oligosaccharides is increased in IBD, especially CD and they recommended the use of lectin enzyme immunoassay for agalactosyl IgG as a novel biomarker for IBD, particularly CD.

Serum soluble ST2 (sST2): ST2 is a member of the interleukin 1 receptor family [62] and sST2 has been introduced as a new and promising activity marker in ulcerative colitis [63].

Lipocalin-2 (LCN2): LCN2 is a potent bacteriostatic protein. In a recent study [64], its serum level was determined in 131 IBD patients (71 with CD, and 60 with UC) and 63 healthy controls. A significant upregulation of serum LCN2 in active IBD compared with healthy controls was confined to active UC. Therefore, this study introduced LCN2 as a marker of UC disease activity.

Other suggested novel biomarkers: Many other markers have been suggested including Soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1) [65], Substance P [66], Activated Thrombin Activatable Fibrinolysis Inhibitor (TAFIa) [67], Quantitative Fecal Immunochemical Test (FITs) [68], fecal Chitinase 3-Like-1 [69], Angiogenin [70], Indoleamine 2,3 Dioxygenase [71], Mucosal cytokine gene expression profiles [72], and Urine Neopterin [73].

Biomarkers of outcomes/complications

Background: IBD particularly UC is precancerous; with the potential of progression to colorectal cancer (CRC) particularly in longstanding cases. Also, IBD particularly CD is associated with a variety of systemic manifestations, including large and small airway involvement. These potential risks illustrate the importance of screening longstanding IBD cases for complications.

Exhaled nitric oxide (eNO): eNO measurement has been suggested in the follow-up of patients with CD to pick up subclinical pulmonary involvement in CD [74].

Fecal pyruvate kinase: Fecal Pyruvate Kinase has been suggested as a potential new marker for intestinal inflammation in children with IBD [75], a new predictor for inflammation and severity of pouchitis [76], and as a new, sensitive screening tool for CRC [77].

miRNAs: PDCD4/miR-21 dysregulation was confirmed in IBD-associated carcinogenesis with miR-21 increases but PDCD4 decreases [78]. Another study [79] confirmed the dynamic changes in the expression of MicroRNA-31 during IBD-associated neoplastic transformation. A third study [80] suggested the detection of miR-92a and miR-21 in stool samples as potential screening biomarkers for CRC and polyps.

Mucosal chitinase 3-like-1: A study by Chen, et al. suggested Chitinase 3-like-1 expression in colonic epithelial cells as a potentially novel marker for colitis-associated neoplasia [81].

Biomarkers of therapy

Background: Some markers are proposed to monitor the effect of the drugs used in treating IBD.

Antibodies to anti-TNF: Secondary loss of response to anti-TNF agents after a period of initial response can be attributed to the formation of anti-drug antibodies that neutralize the drug activities or lead to faster clearance of the drug [82].

A meta-analysis [83] suggested that the presence of antibodies to infliximab (ATIs) is associated with a significantly higher risk of loss of clinical response to infliximab associated with lower serum levels of infliximab in patients with IBD. However, published studies on this topic lack uniform reporting of outcomes and high risk of bias was present in all the included studies.

Therapeutic drug monitoring: Therapeutic drug monitoring in patients with Crohn's disease being treated with adalimumab seems critical. While therapeutic drug monitoring should be performed at trough, a very recent study by Ward, et al. [84] suggested that a drug level ≥4.9 μg/mL obtained during the first 9 days predicts a therapeutic trough drug level with reasonable confidence.

Thiopurine methyltransferase (TPMT) and 6-thioguanine nucleotide (6TGN): Low TPMT activity and high 6TGN concentrations have been linked to therapeutic success in IBD patients treated with thiopurines. However, a recent Spanish study does not support determination of TPMT activity or 6TGN concentrations to predict treatment outcome [85].

Urine Salicylate Level: Mesalamine non-adherence is common among patients with UC which can be difficult to identify in practice. A random urine salicylate level measured in the clinic can identify patients who have not recently taken mesalamine [86].

Genes: Some studies found an association between genetic factors and response to treatment. Polymorphisms in multidrug resistance-1 (MDR1) gene represent a notable example associated with refractory CD and UC. MDR1 polymorphisms is associated with corticosteroid refractoriness in CD and UC, and it is also correlated with a higher risk of cyclosporine failure in patients with steroid-resistant UC [87,88]. Another example is that homozygous carriers of IBD risk-increasing *IL23R* variants are more likely to respond to anti-TNF than homozygous carriers of IBD risk-decreasing *IL23R* variants [8]. A third example is that polymorphisms in apoptosis genes predict

response to infliximab therapy in luminal and fistulizing CD [89].

Conclusion

Currently used IBD markers are far from being ideal. Continuous research for novel markers with ideal characteristics is still required. So, the emergence of novel IBD biomarkers will remain an area of active investigation by enormous number of researchers. An interesting area for this research would be the technology based approach utilizing the advances in genomics, proteomics and metabolomics.

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Austin J Gastroenterol - Volume 4 Issue 2 - 2017
ISSN : 2381-9219 | www.austinpublishinggroup.com

Citation: Bahgat MH and El-Etreby SA. Bio-Markers of Inflammatory Bowel Disease: Past, Present, and Future. Austin J Gastroenterol. 2017; 4(2): 1082.