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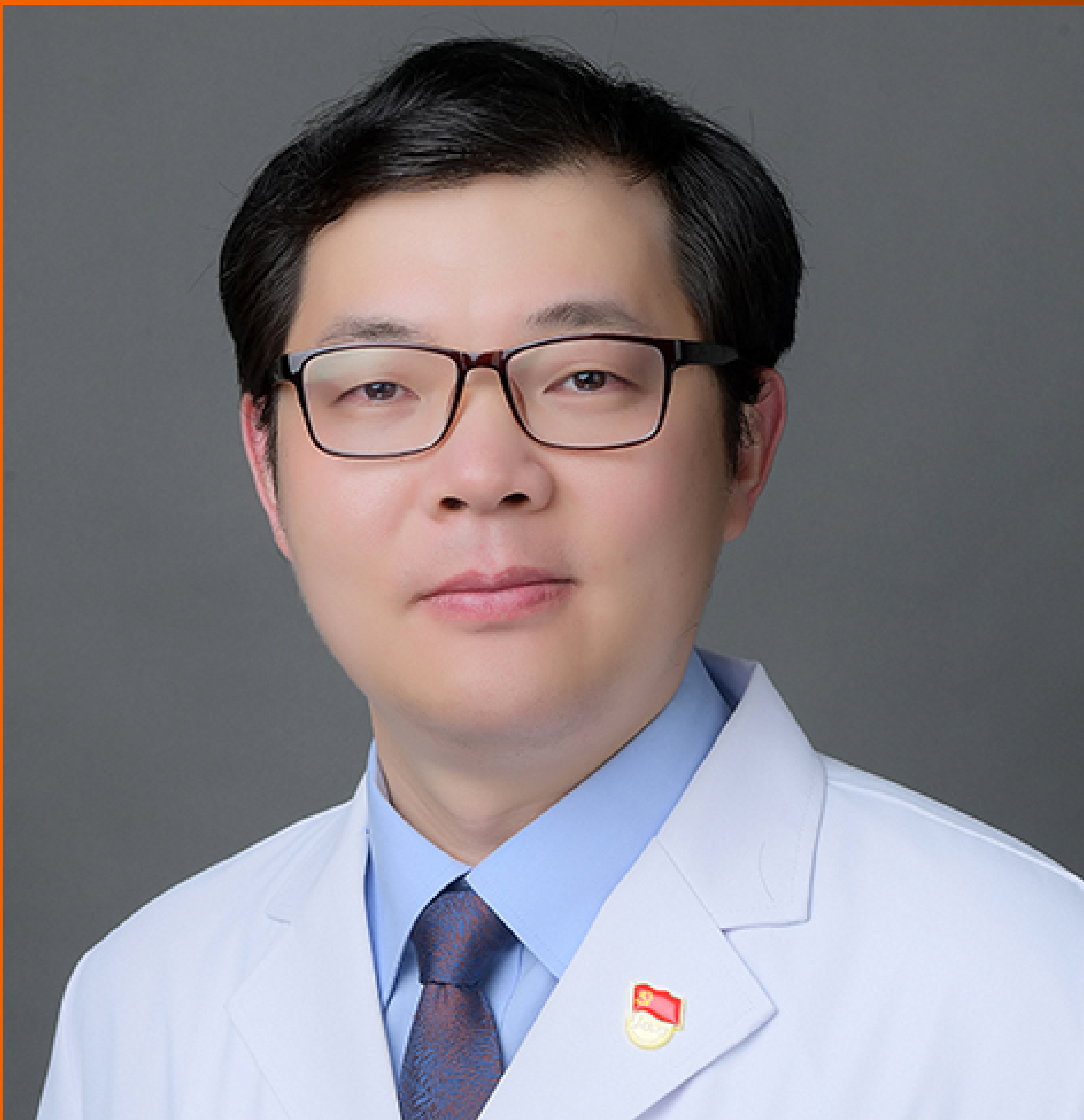

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The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGE mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal endoscopy and covering a wide range of topics including capsule endoscopy, colonoscopy, double-balloon enteroscopy, duodenoscopy, endoscopic retrograde cholangiopancreatography, endosonography, esophagoscopy, gastrointestinal endoscopy, gastroscopy, laparoscopy, natural orifice endoscopic surgery, proctoscopy, and sigmoidoscopy.

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LETTER TO THE EDITOR

Assessing endoscopic remission in small bowel Crohn's disease: Are markers enough?

Iyad A Issa, Taly Issa

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Abstract

Mucosal healing in Crohn's disease (CD) has been established as a crucial target of treatment, leading to long term remission and decrease in complication rates. Endoscopy still serves as the gold standard for assessment, particularly in the small bowel where balloon or capsule enteroscopy is frequently needed. However, these modalities are often unavailable, expensive, and invasive, posing risks to patients. Consequently, the identification of accessible and reliable biomarkers, especially in small intestinal CD, remains a challenge. The study by Ohno *et al*, published in this issue, further illuminates this field. It confirms the potential role of fecal biomarker leucine-rich α2 glycoprotein (LRG) and validates findings from previous smaller trials. Comparing to other markers LRG showed a much higher predictive value for mucosal healing of the small bowel, making it a useful option for small intestinal CD follow up. In this editorial, we explore the optimal marker of inflammation or mucosal healing in CD, particularly in the small bowel. We provide an overview of available conventional biomarkers and introduce several novel biomarkers, including an update on emerging technologies and innovations.

Key Words: Biomarker; C-reactive protein; Crohn's disease; Diagnosis; Fecal calprotectin; Inflammatory bowel disease; Leucine-rich α2 glycoprotein

Core Tip: Small bowel Crohn's disease can be challenging to monitor during treatment. Balloon endoscopy is an invasive procedure, and capsule enteroscopy is costly. The identification of the optimal biomarker remains an ongoing research area. Leucine-rich α2 glycoprotein presents a promising solution, which is discussed in the trial conducted by Ohno *et al*.

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INTRODUCTION

Crohn's disease (CD) is a chronic relapsing inflammatory condition that primarily affects the digestive tract. The underlying pathogenesis remains largely undefined, despite numerous theories proposed over the years. Recent data indicates a continuous and steady rise in CD cases, with a prevalence approaching 1%[1]. CD can potentially impact the entire gastrointestinal tract, causing transmural inflammation of the bowel wall[2]. The primary objective of therapeutic interventions is to induce and maintain remission, while simultaneously preventing long-term complications such as hospitalizations and surgery. Ultimately, the goal is to enhance the overall quality of life. Significant efforts have been invested over the past decade in identifying appropriate and relevant therapeutic targets[3]. The Treat-To-Target approach has gained widespread acceptance and has successfully defined specific therapeutic endpoints within a predetermined time frame[4,5]. Among these targets, mucosal healing (MH) appears to be of paramount importance. Data suggests that mucosal normalization leads to long-term clinical remission and a reduction in intestinal resection rates[6,7].

Nonetheless, the complexity of this issue is further compounded by the absence of a universally accepted definition of MH. Only recently has there been a proposal to include histologic healing in the definition[8]. In a recent trial, Sands *et al* [9] conducted a systematic review of 5530 patients diagnosed with CD, confirming that MH offered patients long-term clinical remission and a reduction in surgery and hospitalization rates. Traditionally, MH has been assessed through ileocolonoscopy, enteroscopy, or small bowel capsule endoscopy[5]. However, these procedures are expensive, invasive, and not readily accessible. Thus, a simpler, cost-effective, and more accessible MH marker is needed.

Biomarkers for CD

The National Institute of Health defines biomarkers as "a characteristic that is objectively measured and evaluated as an indication of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention" [10]. Ideally, biomarkers should possess simplicity, accessibility, non-invasiveness, cost-effectiveness, sensitivity, and specificity to the relevant disease[11]. All biomarkers have advantages and limitations; therefore, a concise summary of the available molecules and those potentially useful in the near future is provided below (Table 1).

Conventional biomarkers

C-reactive protein: Discovered in the 1930s, C-reactive protein (CRP) is an acute phase reactant produced in the liver by interleukin (IL)-6 and secreted during inflammation[12,13]. Widely available in most medical centers, CRP results can be obtained rapidly. While CRP levels increase with inflammation, they also correlate with various other disorders, including infections, autoimmune diseases, and cardiovascular conditions. The accuracy of disease monitoring and MH varies, with stronger correlations observed in CD rather than ulcerative colitis (UC)[14]. Sensitivity of up to 79.5% has been reported[15], although a recent study suggests that this value is primarily applicable to ileocolonic and colonic disease, with significantly lower sensitivity in isolated small bowel CD[16]. Hence, based on the available data, CRP does not appear to be a reliable marker for CD of the small intestine.

Erythrocyte sedimentation rate: Erythrocyte sedimentation rate is a well-established and one of the oldest diagnostic markers, dating back to the 1820s. It has been utilized since then to identify subacute and chronic inflammation[17]. However, its slow regulation in the body and lack of specificity (as it increases during pregnancy, anemia, and various other conditions) render it unsuitable for monitoring CD progression[18].

Fecal calprotectin: Calcium-binding protein, discovered in the 1980s and released by intestinal epithelial cells during inflammation[19,20], is a highly stable molecule. Its secretion in the gut makes it a valuable tool for measuring intestinal inflammation rather than systemic inflammation. Fecal calprotectin (FCP) has been shown to correlate well with gut inflammation, particularly in the colon, with low levels observed during endoscopic and histologic remission[21,22]. Compared to CRP, FCP has demonstrated superior diagnostic accuracy in inflammatory bowel disease (IBD), leading to its increased use in monitoring treatment responses[23]. The International Organization for the Study of IBD recommends an FCP level below 150 micg/g as a reasonable indicator of MH[5]. However, this threshold remains controversial, and no consensus has been reached. A recent systematic review demonstrated the sensitivity and specificity of FCP for endoscopic remission to be 89.7% and 93.3%, respectively, when using a strict cutoff level of 58 micg/g[24]. Another extensive review involving over 1000 patients further confirmed the positive correlation between histologic remission and FCP levels, although the authors emphasized the need for further clarification regarding the optimal cutoff level[25].

Table 1 Biomarkers and their attributes in inflammatory bowel disease

	Marker	Advantages	Limitations
Conventional markers	CRP	Readily available. Cheap. Sensitive for inflammation	Not disease specific. More sensitive for CD than UC. Lower sensitivity for small bowel disease
	ESR	Readily available. Cheap. Sensitive for inflammation	Not disease specific. Elevated in non-inflammatory conditions. More relevant for subacute than acute
	FCP	Readily available. Cheap Sensitive for gut inflammation. Can be used to monitor treatment response	Not specific for IBD. Influenced by external factors (exercise…). Lower sensitivity for small bowel disease
	FIT	Readily available. Cheap. Fair sensitivity for gut inflammation	Low specificity for IBD. Low accuracy for small bowel disease
	LRG	Independent of IL-6. More sensitive for intestinal inflammation than CRP. Acceptable correlation with small bowel disease	Not very cheap. Limited availability
Novel markers	OM	Correlates with inflammation. Can be useful in IBD	Not readily available yet. Not studied for small bowel disease
	FM	Correlates with inflammation. Can be useful in IBD	Not readily available yet. More useful in UC than CD. Not studied for small bowel disease
	F mRNA	Correlates with inflammation. Can be useful in IBD	Expensive. Not tested for small bowel disease
	BAF	Can be useful in IBD. Available data in both UC and CD. Potential role in treatment	Expensive. Not tested for small bowel disease. Not specific to IBD

CRP: C-Reactive protein; ESR: Erythrocyte sedimentation rate; FCP: Fecal calprotectin; FIT: Fecal immunohistochemical test; LRG: Leucine-rich α2 glycoprotein; OM: Oncosttatin M; FM: Fecal myeloperoxidase; Fm RNA: Fecal microRNA; BAF: B-cell activating factor; IBD: Inflammatory bowel disease: UC: Ulcerative colitis; CD: Crohn's disease; IL-6: Interleukin 6.

Conversely, studies have suggested that the accuracy of FCP in predicting MH may be higher for UC compared to CD [24], and even lower for isolated small bowel disease[26]. Furthermore, FCP levels exhibit inter-individual variability, prompting experts to suggest that multiple samples may be necessary on different days[27]. Additionally, dietary factors and exercise can influence FCP levels[28]. So despite its common use and advantages FCP remains far from optimal for use in CD.

Fecal immunohistochemical test: The fecal immunohistochemical test (FIT), commonly employed in primary care as a screening tool for colorectal cancer, detects hemoglobin in the stool[29]. Notably, its additional capability to discern inflammation suggests its potential use as a marker for IBD[30,31]. FIT demonstrated a high sensitivity for diagnosing MH in CD (0.96), although this sensitivity decreased to 0.4 in CD confined to the small bowel[32]. An intriguing hypothesis proposed combining FIT with FCP, which is favored due to its cost-effectiveness. While this combination yielded a robust predictive score for MH, it exhibited a significantly higher predictive value for UC compared to CD[33]. However, it is important to acknowledge the limitations of this approach, including low specificity and questionable accuracy for the small bowel[34].

Leucine rich α2 glycoprotein: A protein that has garnered significant attention and momentum in recent years is leucine-rich α2 glycoprotein (LRG). Secreted by hepatocytes, macrophages, and neutrophils in response to elevated cytokines, LRG has been shown to be elevated in various inflammatory conditions, including primary biliary cirrhosis, rheumatoid arthritis, systemic lupus erythematosus, and IBD during clinical or endoscopic flare-ups[35-38]. Unlike CRP, LRG is not solely dependent on IL-6, suggesting a stronger correlation with intestinal inflammation[39]. Numerous published studies have demonstrated the role of LRG in IBD, with encouraging and positive outcomes[38].

Despite initial conflicting results, more recent studies have confirmed the utility of LRG in CD. One study from Japan validated the predictive ability of LRG for MH with a cut-off value of 16 micg/mL, achieving near-perfect accuracy when the value is below 13 micg/mL[40]. While FCP is an acceptable marker of inflammation in CD, its utility is limited in the small bowel, as previously discussed. This appears not to be the case for LRG, as evidenced by a well-designed trial conducted by Saiki *et al*[41]. In this trial, a small number of CD patients with isolated small bowel disease were identified through gastroscopy, colonoscopy, and capsule enteroscopy. The study found a strong correlation between LRG levels and the extent of mucosal damage in the small intestine. Moreover, the patient population had mild to moderate disease, suggesting that LRG can be utilized in the absence of severe disease.

The current study, published in this issue by Ohno *et al*[42], further reinforces the significance of this marker. Although it employs a retrospective design, the authors include a substantially larger sample size compared to previously published trials. This study reiterates the utility of LRG, particularly in small bowel CD, where other markers demonstrate limitations. Furthermore, it confirms the cut-off level, which appears to be within the range of 12-13 micg/mL (consistent with previous data). While well-designed randomized controlled trials are still necessary, the available data suggest a strong correlation between LRG levels and MH in the small bowel, suggesting it might currently be the most acceptable marker for this patient population.

Novel biomarkers

Oncostatin M: The cytokine family encompasses oncostatin M (OSM), which regulates a diverse range of factors, including IL-6[43]. Elevated OSM levels have been observed in patients with IBD and may correlate with the severity of the disease and the level of inflammation[44]. OSM can be detected in fecal samples and has been demonstrated to be useful in conjunction with FCP[45]. However, to date, there has been no verification of a correlation between OSM levels and isolated small bowel CD.

Fecal myeloperoxidase: Similar to FCP, this fecal neutrophil marker plays a significant role in defending against bacteria while also promoting inflammation[46]. Previous small-scale studies have suggested a role in IBD, particularly in UC[47,48]. A larger study that included both UC and CD patients demonstrated a correlation between disease severity and the marker's performance, comparable to that of FCP[49]. However, the study did not stratify patients based on disease location.

Fecal micoRNAs: Small, non-coding RNAs are present in extracellular fluids and are believed to contribute to inflammation in IBD. Studies have demonstrated their elevated level in the stool of patients with active inflammation[50,51]. Ongoing research suggests a correlation between the level of these RNAs and disease activity in CD patients[52].

B-cell activating factor: A cytokine belonging to the tumor necrosis factor family, B-cell activating factor (BAFF), plays a role in the development of immune cells[53]. Several autoimmune diseases, such as rheumatoid arthritis and Sjogren's syndrome, are associated with elevated BAFF levels[54]. BAFF has been demonstrated to correlate with inflammation in IBD patients, including both UC and CD, with high expression in the intestinal mucosa[55,56]. It is present in feces, serum, and colonic tissues[57]. Furthermore, studies have shown a correlation between BAFF levels and disease activity [55]. Fu *et al*[58] conducted a noteworthy trial in which BAFF was compared to FCP and fecal occult blood test for the prediction of IBD from irritable bowel syndrome (IBS). The results demonstrated that BAFF (levels ≥ 227.3 pg/mL) exhibited superior accuracy in distinguishing IBD from IBS, as well as a higher correlation with the endoscopic inflammatory score in both UC and CD patients. More recent publications have also suggested the potential therapeutic role of BAFF blockade in the management of IBD[59,60]. It appears that this marker will play a significant role in the future diagnosis and potentially treatment of CD patients, although data for small bowel disease remains pending.

Future trends

New markers need proper validation through both large scale pre-clinical and clinical trials to establish and confirm their usefulness. In addition to these novel molecules being studied, newer methods of measuring older markers are currently being developed. For instance, one advancement includes a rapid point-of-care (POC) test for FCP that replaces the time-consuming ELISA technique. A study has demonstrated the rapidity and reasonable agreement of this test with the conventional test[61]. Another novel approach involves a smartphone application that can scan stool and calculate FCP concentration, enabling results for patients at the comfort of their own home[62]. An additional innovation includes a sensor bracelet that can measure CRP and IL-1β levels through sweat gland secretions and provide continuous monitoring throughout the day[63]. Furthermore, there is growing interest in urinary markers as a method for measuring inflammation in IBD, which may provide patients with a more convenient option compared to stool tests, which can often be cumbersome[64].

Artificial intelligence (AI) and machine learning (ML) are revolutionizing various fields, including healthcare. The utilization of AI in the diagnosis and management of IBD has demonstrated remarkable diversity and efficacy[65]. Novel AI-powered programs possess the capability to analyze a comprehensive range of variables, including biomarkers, symptoms, radiologic, and endoscopic images, with the aim of predicting flare-ups and subsequently generating precise, personalized treatment plans tailored to individual patients[66]. One notable example is the application of support vector machines (SVM), an AI model capable of predicting the disease course and response to therapy by analyzing a multitude of subjective and objective variables. Consequently, personalized medical protocols are generated[67]. Several ML models have been developed, but the SVM model appears to be particularly impressive, exhibiting notable performance in predicting inflammation scores among patients with CD, with sensitivity of 0.95, specificity of 0.92, and accuracy of 0.93[68]. As with any innovation or technological advancement, including the development of new devices, it is imperative to acknowledge the potential limitations, particularly ethical and patient privacy concerns. Consequently, it is crucial to draft appropriate legislation and enforce rigorous validation studies to ensure the safety and efficacy of these technologies.

CONCLUSION

The treatment of CD has undergone significant advancements over the past decade, resulting in improved outcomes and increased rates of remission with reduced disease-related morbidity. However, follow-up of patients with small bowel CD remains challenging for physicians. The available modalities are invasive and costly, and the current biomarkers are not yet optimal. LRG offers a novel potential, sensitive, and specific option for this subtype of patient population. The study by Ohno *et al*[42] confirms previous encouraging results and defines the suspected cut-off level in a retrospective trial with a relatively large patient cohort. Nevertheless, prospective randomized trials are still necessary to validate this marker and incorporate it into our diagnostic arsenal. With the advent of AI and deep learning models, the progression of methods for diagnosing and managing IBD patients will be highly exciting to observe in the coming years.

FOOTNOTES

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