EDITORIAL

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Which biomarkers best reflect the degree of inflammation in Crohn's disease?

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Article: Combination of leucine-rich alpha-2 glycoprotein and fecal markers detect Crohn's disease activity confirmed by balloon-assisted enteroscopy **(Intest Res 2024;22:65-74)**

Leucine-rich alpha-2 glycoprotein (LRG) has emerged as a novel serum biomarker for the diagnosis, monitoring disease activity, and predicting prognosis in various chronic diseases.[1] LRG, an interleukin-6 (IL-6)-independent glycoprotein, is identified through the isobaric tags for relative and absolute quantification proteomic approach in patients with rheumatoid arthritis.[2] C-reactive protein (CRP) is the most commonly used serum inflammatory marker, upregulated by IL-6 and produced locally in inflamed or damaged tissue. LRG is regulated by IL-6 as well as other pro-inflammatory cytokines and is produced by inflamed organs, neutrophils, macrophages, intestinal epithelial cells, and hepatocytes.[3] While strong inhibition of IL-6 function normalizes CRP, LRG may not be suppressed and is expected to better reflect inflammation. Therefore, LRG is suggested as a promising biomarker that could reflect disease activity more effectively than CRP.

Crohn's disease (CD) is a chronic inflammation of the gastrointestinal tract. The clinical course of CD can vary from a quiescent course with clinical remission to fulminant disease requiring surgery.[4] The treat-to-target strategy for inflammatory bowel diseases, as proposed by the International Organization for the Study of Inflammatory Bowel Diseases, includes clinical remission and normalization of CRP and fecal calprotectin as short-term and intermediate-term treatment targets.[5] Long-term treatment targets also encompass endoscopic mucosal healing, improved quality of life, and the absence of disability.[5] Therefore, regular monitoring of symptom, laboratory results, endoscopy, and cross-sectional imaging is crucial for CD patients. While endoscopy can directly confirm mucosal healing in colonic CD patients, monitoring of mucosal healing in small bowel CD patients poses a challenge. Video capsule endoscopy and device-assisted endoscopy (DAE) provide visualization of entire small intestine, but video capsule endoscopy is not suitable for structuring CD patients and DAE is not ideal for regular monitoring due to its invasiveness. Serologic monitoring, including CRP and fecal calprotectin, is an alternative, but the correlation between serologic examinations and mucosal healing varies.[6] Fecal calprotectin significantly correlates with mucosal healing at the colon location but not in the small bowel, according to previous studies.[7] Therefore, there is an unmet need to discover a new noninvasive monitoring biomarker for intermediate targets with higher accuracy in assessing mucosal healing.

Recently, LRG has been investigated as a noninvasive monitoring biomarker in CD patients. Yasutomi et al.[8] reported a significant correlation between LRG and endoscopic disease activity in CD patients, which is equivalent to CRP and fecal calprotectin. In the subgroup analysis based on disease location, colonic CD patients exhibited a stronger positive correlation between LRG and endoscopic disease activity compared to ileal CD patients.[8] Based on these results, it appears that in

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patients with CD, inflammatory biomarkers may be less reliable for identifying mucosal healing in the small bowel than in the colon.

Kawamura et al.[9] also reported a significant correlation between LRG and endoscopy disease activity as assessed by DAE in CD patients. In the subgroup analysis considering disease location, both colonic CD and small bowel CD patients demonstrated a positive correlation between LRG levels and applied Simple Endoscopic Score for CD score.[9] In the subgroup analysis based on disease severity, serum LRG levels significantly increased with higher endoscopic disease activity score.[9] Additionally, LRG, rather than CRP, albumin, and Crohn's Disease Activity Index, emerged as the only independent factor associated with endoscopic remission. However, it is worth noting that this study did not assess the relationship between LRG and fecal calprotectin.

In the current issue, a study examined the correlation between endoscopy disease activity and hemoglobin, platelet count, CRP, fecal calprotectin, fecal hemoglobin, and LRG in patients with ileal and ileocolonic type CD.[10] The results revealed that LRG and fecal calprotectin emerged as the most effective biomarkers for assessing mucosal healing in small bowel CD in this study.[10] Furthermore, this article suggested that dual positivity for LRG and fecal calprotectin, as well as LRG and fecal hemoglobin, can enhance the correlation with endoscopy disease activity and predict the prognosis of CD, including factors such as hospitalization, surgery, and relapse.[10]

ADDITIONAL INFORMATION

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Conflict of Interest

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