EDITORIAL

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Could histologic healing be a new treatment target in patients with ulcerative colitis?

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See Article on Page 68-76

Ulcerative colitis (UC) is one of the inflammatory bowel diseases (IBDs), all of which are characterized by chronic relapse and remission. The chronic nature of UC can impose a considerable disease burden on patients and substantially reduce their quality of life [1]. Regular monitoring of patients with UC is crucial to manage disease activity. The Selecting Therapeutic Targets in Inflammatory Bowel Disease-II (STRIDE-II) study has proposed immediate, intermediate, and long-term treatment targets with the aim of improving the management of patients with IBD. These targets include a clinical response or remission, the normalization of C-reactive protein and fecal calprotectin levels, and endoscopic healing [2].

Recently, histologic healing has been proposed as an additional treatment target for UC. Seong et al. [3] demonstrated that histologic activity, defined as a Geboes score ≥ 3.1, is independently associated with clinical relapse in UC patients with a Mayo endoscopic subscore (MES) of 0 or 1. Jangi et al. [4] found that achieving histological remission, defined as either complete mucosal normalization with no epithelial neutrophils or chronic architectural changes with ≤ 1 neutrophil per high power field in the lamina propria, was associated with better outcomes, including a lower risk of clinical relapse and hospitalizations in patients with UC treated-to-target of endoscopic healing. However, the STRIDE-II consensus did not endorse histologic healing as a formal treatment target, although it recognized histologic healing as a potentially important adjunctive measure in UC [2].

In their study published in this issue of the *Korean Journal of Internal Medicine*, Shin et al. [5] prospectively evaluated the histologic features predicting prognosis and analyzed the endoscopic findings that correlated with active histologic inflammation in UC patients with complete or partial mucosal healing. Two or more biopsy samples were obtained from the most severely inflamed lesion in each segment; in cases with no inflammation, two biopsy samples were obtained from the sigmoid colon and rectum. Histologic activity was assessed using the Nancy index (NI), and additional histological evaluation was performed by referring to other reliable intra- and interobserver histological measures, including the Robarts histopathology index, the Geboes score, and the Riley score [6]. During the follow-up period, disease progression was observed only in patients with an MES of 1; none of the patients with an MES of 0 exhibited disease progression. A significant correlation was determined between an NI ≥ 3 and disease progression ($p = 0.009$, Kaplan–Meier curves). Mucosal friability on endoscopy was significantly associated with an NI ≥ 3 (61.1% for NI < 3 vs. 88.0% for NI ≥ 3; $p = 0.013$). The authors suggested that UC patients with more severe histologic activity or mucosal friability on endoscopy require closer monitoring, even if they only have mild endoscopic activity.

The strengths of the study lie in its prospective design, ideally obtained biopsy specimens, assessment of histologic activity with validated histologic scoring systems, and focus on patients with mild endoscopic activity. However, the authors also noted certain limitations, including the fact that their study used a single-center design, the sample size was relatively small, and long-term follow-up data were lacking. In addition, patients with proctitis were included, which may have lowered the disease progression rate.

The added value of histologic healing over endoscopic healing in predicting prognosis, such as long-term remission [7,8], as well as for cancer prevention [9], has been well

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demonstrated in UC [10]. Histologic remission is a desirable therapeutic goal to prevent long-term complications [2]. Nevertheless, histologic healing is not a feasible treatment target in all patients. Obtaining a mucosal biopsy requires subjective decisions on biopsy location; moreover, the optimal number of specimens is unclear, interpretation of the findings by pathologists is often delayed, and the biopsy itself is invasive and costly [10]. Consequently, the risks and benefits must be carefully weighed. In addition, the lack of standardized reporting protocols limits the clinical utility of histological remission [2,10]. With continuing advances in computer-aided diagnostic systems that predict histologic activity, there will be less need for biopsies and therefore also for the opinion of expert pathologists, which will reduce costs. These systems will also facilitate the establishment of reproducible and standardized reporting methods [10,11]. In the meantime, further large-scale, multi-center, long-term studies are necessary to develop a standardized histological remission assessment system and to determine the benefits of histologic healing relative to the risks and costs.

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