Histologic Markers of Inflammation in Patients With Ulcerative Colitis in Clinical Remission

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BACKGROUND & AIMS: **Mucosal healing, based on histologic analysis, is an end point of maintenance therapy for patients with ulcerative colitis (UC). There are few data on how histologic signs of inflammation correlate with endoscopic and peripheral blood measures of inflammation in these patients. We investigated patterns of histologic features of inflammation in patients with UC in clinical remission, and correlated these with endoscopic and biochemical measures of inflammation.**

METHODS: **We performed a prospective observational study of 103 patients with UC in clinical remission undergoing surveillance colonoscopy while receiving maintenance therapy with mesalamine or thiopurines; 2674 biopsy specimens were collected from 708 colonic segments. Each colonic segment was evaluated based on the Mayo endoscopic subscore and the Geboes histology score (range, 0−5.4). Biomarkers were measured in peripheral blood samples.**

RESULTS: **Histologic features of inflammation were found in 54% of patients receiving maintenance therapy; 37% had at least moderate inflammation based on histology scores. Of the 52 patients with endoscopic evidence only of left-sided colitis, 34% had histologic features of inflammation in their proximal colon. Histology scores correlated with endoscopic scores for per-segment inflammation (Spearman $\rho = 0.65$; $P < .001$). Patients with histology scores greater than 3.1 had a significantly higher mean level of C-reactive protein than those with scores less than 3.1. There were no differences among treatment groups in percentages of patients with histologic scores greater than 3.1.**

CONCLUSIONS: **Patients in clinical remission from UC still frequently have histologic features of inflammation, which correlate with endoscopic appearance. Patients with at least moderate levels of inflammation, based on histologic grading (score >3.1), have higher serum levels of C-reactive protein, which could be used as a surrogate marker of histologic inflammation.**

Keywords: Mesalamine; Response to Therapy; Therapeutic Efficacy; Mucosal Healing; IBD.

The goal of therapy in patients with ulcerative colitis (UC) has shifted from symptom control alone to clinical remission in conjunction with mucosal healing.[1] Clinical trials of drugs in patients with UC now routinely include a mucosal healing end point, and expert consensus recommends healing as an end point for optimal management in practice.[2] The advantages of achieving resolution of mucosal inflammation can be seen in the reported lower rates of disease relapse, hospitalization, need for immunosuppressive therapy, and colon cancer in patients who obtain mucosal healing.[3–5]

Although most studies on mucosal healing focus on endoscopic scores, such as the Mayo subscore, some experts have suggested histologic inflammation may be a valuable goal of therapy.[6,7] The presence of histologic inflammation is a better predictor of future clinical relapse than endoscopic appearance alone.[8] A higher risk of relapse was noted in studies of patients with persistent active microscopic inflammation when compared with patients with normal histology.[9–11] Histologic remission also was associated with a lower rate of hospitalization during a median 29-month follow-up evaluation in a small cohort.[12] A recent abstract from Rubin et al[11] reported that an increased level of histologic inflammation could predict both colectomy and hospitalization in patients with UC.

In this context, validated scoring systems for the evaluation of histologic severity in clinical trials are desirable. The Riley index, Geboes index, and Chicago index have been developed for this purpose, but none are universally used or have been

Abbreviations used in this paper: Aza, azathioprine; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; 6-MP, 6-mercaptopurine; UC, ulcerative colitis.

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independently validated.[10,11,13] Recent expert guidelines have recommended a histologic score be applied consistently as a secondary end point in clinical trials.[6] The Geboes score was first reported in 2000; it showed good reproducibility and modest agreement with the endoscopic grading system in 28 patients. Its independent validation has not been reported since then.

Evaluation of the severity of histologic inflammation as an end point for drug therapy has not been part of standard clinical practice, although persistent endoscopic and histologic inflammation in the absence of clinical symptoms is common.[14,15] Patients with quiescent UC with histologic inflammation are difficult to identify because endoscopic measures of inflammation have a variable correlation with symptoms. A small prospective study, presented only in abstract form, reported only modest agreement between clinical, endoscopic, and histologic measures of remission with complete agreement in just 58% of 91 patients (kappa, 0.44) and 89% agreement between endoscopy and histology.[16] Given the potential importance of histologic healing in long-term outcomes with UC, and the limitations of using symptoms alone to screen for underlying macroscopic or microscopic inflammation, identification of markers of histologic inflammation are needed for patients in remission.

The goal of this study was to enroll a cohort of patients with UC in clinical remission, to determine the prevalence of histologic colitis in these patients using the Geboes grading system, and to compare the correlation between the Geboes score and endoscopic and biochemical markers of disease activity in this setting.

Materials and Methods

This was a prospective observational study performed at a single tertiary referral center. The study was approved for enrollment of human subjects by the local Institutional Review Board (protocol #2009-P-000314). All patients with a confirmed history of UC who attended the endoscopy unit for a clinically indicated surveillance colonoscopy were screened. All patients received the same bowel preparation (magnesium citrate). Clinical disease activity was determined using the Simple Clinical Colitis Activity Index, a validated score of colitis activity that has been shown to correlate well with endoscopic indexes.[17,18] To be considered "in remission" for enrollment in this study, participants had to have a Simple Clinical Colitis Activity Index score less than 2.5 at the screening visit, and have had no changes in their UC medications or any steroid use in the prior month.[17]

Each enrolled patient had baseline demographic and ulcerative colitis disease history recorded. This included disease location, duration, prior and current medication use, family history, extraintestinal disease, smoking status, and nonsteroidal anti-inflammatory drug use. During the index colonoscopy, the colon was divided into 8 segments (cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, and rectum). Endoscopic activity in each colonic segment was classified by the endoscopist using the sigmoidoscopy subscore of the Mayo activity index (Supplementary Table 1).[19] A subset of 15 patients had their endoscopy images re-scored by a second blinded endoscopist to determine the interobserver agreement for the endoscopic score. The κ statistic was 0.7, suggesting substantial agreement between endoscopists.

The protocol for the 4 gastroenterologists who performed the colonoscopies included the recommended 4-quadrant biopsies every 10 cm. Histologic activity in all segments was classified using the Geboes scale, by a gastrointestinal pathologist (J.D.G.) blinded to the patient's disease status and endoscopic scores.[13] A baseline blood sample was drawn for measurement of white blood count, hematocrit (Hct), erythrocyte sedimentation rate (ESR) (in mm/h), and C-reactive protein (CRP) (in mg/L) in all patients.

Histologic Scoring

The Geboes grading system is an instrument with 6 domains: structural (architectural change), chronic inflammatory infiltrate, lamina propria neutrophils and eosinophils, neutrophils in epithelium, crypt destruction, and erosions or ulcerations.[13] Scores can range from 0 to 5.4, with higher scores indicating more severe histologic inflammation (Supplementary Figure 1). A total Geboes score was assigned to biopsy specimens from each colonic segment and the highest score (most inflamed segment by histology) was used as the total histology score for each patient.

Statistical Analysis

Dichotomous variables were analyzed for outcomes using the chi-square test or the Fisher exact test where appropriate, and continuous variables were analyzed using the *t* test if normally distributed, or the Wilcoxon test for non-normal data. Correlation between ordinal numeric scores was analyzed by the Spearman rank correlation coefficient (ρ). A κ agreement statistic was generated for assessment of dichotomous characterization of normal/not normal by endoscopic and histologic scores. Data were analyzed with JMP 8.0 (SAS Institute, Inc, Cary, NC). Post hoc power calculations were performed using the PS Power and sample size calculator (available at: http://biostat.mc.vanderbilt.edu/PowerSampleSize).

Results

A total of 147 patients scheduled for surveillance were screened, and 103 were enrolled in the study. Only 10% of the eligible population screen-failed as a result of clinically active disease at the time of colonoscopy. The baseline characteristics of these 103 patients are summarized in Table 1, and were similar to our typical surveillance population. The biopsy sampling protocol during surveillance was extensive; the mean number of biopsy specimens per colonoscopy was 26, and 2674 biopsy specimens in total were taken during the 103 colonoscopies.

Of the 103 colonoscopies, 54% of patients had at least one biopsy specimen with evidence of any histologic inflammation, and 37% had biopsy specimens that met the Geboes criteria for abnormal histologic inflammation (score $\geq$3.1).[20] Eleven patients (11%) had a colonoscopy that showed histologic inflammation in the right colon (score $>$0) in the absence of endoscopic inflammation, and 6 of these patients had scores of 3.1 or greater. Of the 52 patients with endoscopic evidence only of left-sided colitis, 34% had histologic inflammation in their right colon.

Among all colonic segments (n = 708), 20% had histologic evidence of inflammation, and 21% had an abnormal endo-