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Histologic Remission: The Ultimate Therapeutic Goal in Ulcerative Colitis?

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Ulcerative colitis (UC) is a disease of the mucosal layer, and activity of the disease is assumed to be related to mucosal appearance. Mucosal healing has emerged as a major therapeutic goal in UC. Whether mucosal healing should be the ultimate therapeutic goal in these patients is unknown. Even when endoscopy suggests mucosal healing, evidence of histologic activity has been observed. Histologic healing requires complete recovery of the colonic mucosa, with absence of inflammation or structural changes. Histologic improvements have been linked with improved clinical outcomes, such as a reduced risk of relapse and need for surgery/hospitalization and a reduced risk of developing cancer. Hence, there is a rationale for aiming for histologic remission in UC. Numerous methods of classification of histologic activity in UC have been proposed, although only some of these are widely used. We review the current definitions of histologic remission, the range of scoring systems most commonly used, and the evidence of histologic improvement that is available from the latest therapies for UC. We also highlight questions that will require careful consideration if histologic remission is to become more widely used as an end point in clinical trials and a treatment goal in clinical practice.

Keywords: Inflammatory Bowel Disease; Histologic Assessment; Disease Modification.

In patients with ulcerative colitis (UC), mucosal healing, routinely assessed by endoscopy, has emerged as a major therapeutic goal because the inflammation is limited to the mucosal layer.[1] Mucosal healing is not always an accurate indicator of histologic healing because microscopic evidence of inflammation is common even in patients with clinically and sigmoidoscopically quiescent colitis.[2] Several articles have evaluated the importance of mucosal healing in UC; however, they did not evaluate histologic healing.[3–5]

Historically, a poor correlation has been found between histologic findings and indices of activity for UC, with abnormal histologic findings observed in a large number of patients with UC in clinical and endoscopic remission.[2,6–9] Microscopic features of activity may persist in macroscopically inactive disease, suggesting that endoscopy may underestimate the extent of the disease.[7,10–13] A better correlation is found between endoscopy and histology when the samples are obtained during active inflammation.[14] Accumulating evidence indicates that histologic healing may be associated with better clinical outcomes in UC and could represent the ultimate therapeutic goal in UC.[7,15]

Herein, we review current definitions of histologic remission and healing, available histologic scores, the impact of histologic remission on outcomes in UC, and the efficacy of UC-related medications in achieving histologic remission.

Defining Histologic Remission and Healing

Some clinical studies refer to "histologic remission" as an end point,[16–18] although many use the term "histologic improvement,"[19,20] often because the therapy under investigation was not efficacious enough to achieve histologic remission and healing. In contrast, Korelitz[7] and Gheorghe et al[21] have used the term "histologic healing." Histologic healing has not been used in clinical decision making, partly because histologic changes often take longer to appear than clinical or endoscopic improvements,[14,22] and partly because it has been questioned whether histologic remission is a realistic treatment goal with currently available treatment options and whether it is practical to implement in daily practice. D'Haens et al[14] recommended that histologic remission should not be used as a primary end point for therapeutic efficacy, but instead should be considered as a secondary end point.

There seems to be confusion around the more commonly used term "mucosal healing", and whether histologic healing forms a part of it. In 2007, the International Organization for the Study of Inflammatory Bowel Disease defined mucosal healing as the absence of friability, blood, erosions, and ulcers in all visualized segments of the gut mucosa, excluding histologic healing from this definition.[14] By contrast, Lichtenstein and

Abbreviations used in this paper: **CI, confidence interval; OR, odds ratio; UC, ulcerative colitis.**

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Rutgeerts[23] defined it as the absence of all mucosal ulceration, both microscopic and macroscopic, providing a sigmoidoscopy score of 0, as assessed by the Ulcerative Colitis Disease Activity Index. Other researchers used the term "mucosal healing" to describe complete recovery of the colonic mucosa, comprising both endoscopic and histologic healing.[21,24] In more recent clinical trials assessing the efficacy of biologics in UC, mucosal healing was defined by achieving a Mayo endoscopic subscore of 0 or 1, excluding histologic healing.[25] In contrast, Korelitz[7] argued that histologic healing should be a minimal criterion for mucosal healing. Gheorghe et al[21] defined histologic healing as the absence of residual mucosal inflammation with distinctive changes in crypt architectural distortion and/or atrophy, or completely normal mucosa.[26]

Methods Used to Measure Histologic Activity and Categorize Histologic Remission

Histologic features of UC are well documented, comprising mild, moderate, or severe inflammatory activity that results in distortion of the architecture of the mucosal lining of the colon (Supplementary Figures 1 and 2).[27] A standard system for grading histologic activity does not exist[28] and numerous methods of classification of histologic activity have been proposed (Table 1).[2,8,10,12,14,29–31] None of these scores has been validated. Validation is a prerequisite for using one of the scores to standardize reporting and grading. These scores are based on H&E readings. Whether this is the optimal method will require further investigation because other techniques, such as immune histochemistry for myeloperoxidase, may be more accurate. Furthermore, it should be noted that various factors can affect histologic features when evaluating histologic healing. These include timing of the biopsy (ie, newly diagnosed vs chronic disease), site of biopsy (eg, rectal therapy may normalize rectal histology whereas more proximal colon remains histologically active), and patchy healing (resulting from the natural history of UC or multiple medical therapies).

Impact of Histologic Remission on Clinical Outcomes in Ulcerative Colitis

Several studies have shown that histologic healing is associated with favorable clinical outcomes and is a negative predictor of relapse in patients with UC and of colon cancer risk (Figure 1).[2,15,24,29] The presence of histologic healing may define a subset of patients with UC in whom treatment can be withdrawn.[21] An early study found that 57.9% of patients with no significant histologic inflammation after a course of corticosteroids were symptom-free over the course of 1 year, compared with 16.7% of patients with evidence of inflammation on a rectal biopsy.[24]

Histologic healing may be a better predictor of time to relapse than macroscopic appearance or clinical criteria.[15] In a study of 82 patients with UC in symptomatic and sigmoidoscopic remission, an acute inflammatory cell infiltrate, the presence of crypt abscesses, and mucin depletion were associated with increased risk of relapse.[2] Acute inflammatory indicators were associated with a 2- to 3-fold increased risk of colitis during 12 months of follow-up evaluation. Bitton et al[32] did not replicate the findings of Riley et al[2]; however, their multivariate analysis of data in 74 patients with inactive UC identified an association between basal plasmacytosis (a dense infiltration of plasma cells extending into the lower third of the lamina propria) and shorter time to relapse. There are some indications that eosinophils may predict relapse, but this has not been studied in any depth. In a small, prospective study of 26 patients with quiescent UC, increased numbers of neutrophils and eosinophils in the lamina propria were more frequent in relapsers than nonrelapsers. An increase in basal lymphoid aggregates in relapsers was observed, similar to the findings of Bitton et al,[32] but did not reach statistical significance.[33] Most recently, in a retrospective analysis of a cohort of 75 patients with UC, Bessissow et al[34] showed that despite normal endoscopy, histologic investigation showed inflammatory activity (Geboes score, $\geq$3.1) in 40% of patients, and basal plasmacytosis in 21% of patients. Clinical relapse was observed in 20% (n = 15) of patients at 12 months. Using multivariate analysis, the presence of basal plasmacytosis predicted UC clinical relapse (odds ratio [OR], 5.13; 95% confidence interval [CI], 1.32–19.99; $P = .019$) in these patients with complete mucosal healing.

Histologic predictors of medically refractory UC also have been investigated. One study observed that lymphoid follicles were predictive of medically refractory UC in patients aged 38 years or younger, whereas severe cryptitis was predictive in patients aged older than 38 years.[35] Furthermore, preliminary data have suggested that increased histologic inflammation is predictive of increased risk of colectomy and hospitalization in patients with UC.[23] Similarly, in a large cohort of UC patients in a colonoscopic surveillance program, higher mean inflammation score was a significant predictor of colectomy.[36] Further evidence from a small cohort study of patients with UC has shown histologic remission to be associated with a lower rate of hospitalization (OR, 0.27; 95% CI, 0.07–0.95; $P = .048$).[15,37]

Histologic remission also correlates with a reduction in colorectal cancer risk. An epidemiologic case-control study of 68 UC patients and 136 controls observed an association between histologic inflammation score and the risk of colorectal cancer by both univariate and multivariate analyses (OR, 4.69; 95% CI, 2.10–10.47; $P < .001$).[38] Similarly, a cohort study of 418 patients determined that the severity of histologic inflammation