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Follow-Up of Ulcerative Colitis Patients Who Have Achieved Histological Normalization

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Keywords

Histological normalization; Inflammatory bowel disease; ulcerative colitis

Introduction

The natural history of ulcerative colitis (UC) follows a relapsing and remitting course of inflammation and is accompanied by associated mucosal injury and historically, microscopic features of chronicity that were the sine qua non for the diagnosis [1]. As goals for the management of UC have evolved to include objectively measured endoscopic improvement of the mucosa, there also has been a move to include histological endpoints in assessment of disease activity [2,3]. However, there remain a number of unanswered questions about histology in UC and this is not yet a specific treatment goal [4].

We recently reported the association of histological activity and both clinical and endoscopic activity in patients with UC, as well as the clinical outcomes of these patients [2]. In this study of 646 patients with confirmed UC we included a previously undescribed histologic endpoint of “normalization,” (Hn) in which there were no features of acute or chronic inflammation. Importantly, with median 22 months of clinical follow-up, the patients with Hn were less likely to suffer a clinical relapse than patients with histological inflammation or even histological quiescence. Here, we report the subsequent longer term follow-up of the subset of UC patients who achieved Hn and describe their clinical and histologic progression.

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Author contributions: DTR conceived and designed the study. AI drafted the manuscript, with critical revisions from DTR, BC, JO, RDC, SD and AS. AI, KE and VR did the data collection and contributed to the data analysis and interpretation. All authors approved the final version of the manuscript.

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Methods

This is an IRB-approved retrospective review from our tertiary inflammatory bowel disease (IBD) center of adult patients with confirmed UC who had Hn on endoscopic colon biopsies taken between August 2005 and October 2013. These patients were followed out to October 2018. Demographic and disease-related information was collected from our institutional database. We assessed prior and subsequent reports from pathology using our previously described 6-point scoring system and categorized tissue as normal (score=0), quiescent (score=1) or active (score =1=2) [5]. We also reviewed all subsequent clinical notes to evaluate for clinical relapse.

Results

We identified 30 UC patients [13 men (40%)] with Hn of the colorectum who had at least one subsequent clinical or histological assessment. The median age at UC diagnosis was 25 years (y) $\pm$ 15.3 and the median age at Hn index was 41.5 y $\pm$ 15.4. The disease distribution by Montreal classification was 6 (20%) E1, 5 (17%) E2 and 19 (63%) E3. Median follow-up time was 5.16 y (range 1.13–14.19).

Of the 29 of 30 patients who had clinical follow-up, 19 (66%) remained inactive and 10 (33%) had a clinical relapse [median 4.9 y (range 1.13–14.19)]. The percent of patients without relapse noted on the Kaplan-Meier curve was less than 50% over the entire duration of follow up and over 90% in the first 1 year (Fig 1). After normalization, ten of these 29 patients underwent medical de-escalation of therapy, 1 had change within class, and 3 had medical escalation. Of the 18 of 30 patients who had histological follow-up, 6 (33%) maintained Hn for median 6 y $\pm$ 2.8 y follow-up, 9 (50%) became quiescent then reverted back to Hn, 2 (11%) became quiescent and remained quiescent, and 1 (5.5%) became histologically active (Fig 2). Six of these 18 patients underwent medical de-escalation of therapy, 1 had change within class, and 3 had medical escalation. Two (33%) maintained Hn, 2 (33%) became quiescent then reverted back to Hn, 1 (17%) became quiescent and remained quiescent, and 1 (17%) became histologically active.

Discussion

In recent years, histological healing has been increasingly discussed as a possible target in achieving remission with the notion that healing the bowel beyond what is seen on endoscopy may provide additional benefit. While there has been evidence demonstrating that histologic inflammation is associated with increased risk of clinical relapse, hospitalization, surgery, and colorectal cancer [6,7], the characteristics and natural history of UC patients who achieve normalization has not been previously described. In this small observational cohort of patients with UC who have achieved Hn, one-third appear to have stable disease, but in follow-up, a majority had subsequently identified histological findings of classical quiescence, suggesting that the prior normalization finding is either transient or may have been a sampling or interpretation error. The variation in number of endoscopies per patients in study may have contributed to this finding. Histologically active inflammation and clinical relapse were rare but did occur. Although the small number and retrospective

nature were limitations, this is the first long-term follow-up of Hn patients to exist in the literature. These findings demonstrate that a single finding of Hn is associated with favorable prognosis, but that Hn does not represent cure. Further research in this endpoint and in therapeutic de-escalation and monitoring of these patients is warranted.

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Abbreviations:

Hn	Histological normalization
IBD	Inflammatory bowel disease
UC	ulcerative colitis

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Figure 1: Kaplan-Meier curve for relapse in UC patients subsequent to demonstrating colonic histologic normalization(Hn). The line represents the proportion of patients not experiencing clinical relapse among patients with Hn at the end of follow up.

Figure 2:

Follow-up of histological disease activity in UC patients who have achieved histologic normalization. Year 0 is time of indexed normalization date. Histology scores: 0=normal, 1=quiescent, 2=active.