Endoscopic Assessment and Treating to Target Increase the Likelihood of Mucosal Healing in Patients With Crohn's Disease

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BACKGROUND & AIMS: **Mucosal healing has been proposed as a goal for treatment because it is associated with improved clinical outcomes of patients with Crohn's disease (CD). However, little is known about the feasibility or probability of achieving mucosal healing in clinical practice. We evaluated the feasibility of treating patients to achieve mucosal healing based on endoscopic evaluation (treating to target).**

METHODS: **We reviewed the endoscopic outcomes of 67 patients with CD who had lesions detected by endoscopy. Patients underwent 2 to 4 subsequent endoscopic evaluations at the University of California San Diego and were followed up from 2011 through 2012; data were collected on therapies and patient management. The cumulative incidences of mucosal healing and endoscopic improvement were estimated using the Kaplan–Meier method. Factors independently associated with mucosal healing were identified using a Cox proportional hazards model.**

RESULTS: **After a median follow-up period of 62 weeks, 34 patients (50.7%) had mucosal healing and 41 patients (61.1%) had endoscopic improvement. The cumulative probabilities of mucosal healing were 12.7% and 45.0% at 24 and 52 weeks of treatment, respectively. Factors associated with mucosal healing were as follows: fewer than 26 weeks between endoscopic procedures (hazard ratio, 2.35; 95% confidence interval, 1.15–4.97; $P = .035$) and adjustment to medical therapy when mucosal healing was not observed (hazard ratio, 4.28; 95% confidence interval, 1.9–11.5; $P = .0003$).**

CONCLUSIONS: **In an endoscopic study of patients with CD, we found that assessment of endoscopic disease activity and adjustments to medical therapy (treat to target) increase the likelihood of mucosal healing.**

Keywords: Treat-to-Target; Prognostic Factor; Ulcer Detection; Inflammatory Bowel Disease.

Crohn's disease (CD) is a chronic but dynamic inflammatory disease of the gastrointestinal tract that leads to progressive bowel damage. Current evidence suggests that treatment strategies aimed at controlling symptoms do not alter the course of CD.[1,2] The natural history of CD, as defined by population-based cohort studies from the past 30 years, is a progression from inflammatory disease to the development of complications such as stricture, fistula, abscess, and, ultimately, the requirement of surgery in a majority of patients.[3,4] The medical management of CD and the treatment goals at that time, which were based exclusively on control of symptoms and relied heavily on corticosteroids, were unable to prevent bowel damage or slow the progressive destructive course of the disease in the majority of patients.[5]

Based on this unfavorable natural history, and the introduction of immunosuppressives and biologics into clinical practice, new therapeutic goals and strategies that potentially could reduce complications and thus modify the course of the disease have emerged. Subsequently, the idea of mucosal healing (MH) as a treatment goal began to receive increasing attention after studies showed that it might improve long-term clinical outcomes. For example, among 130 cases in the Inflammatory Bowel Disease in South-Eastern Norway (IBSEN) population-based cohort of patients with newly diagnosed CD who had endoscopy follow-up evaluation, the

Abbreviations used in this paper: CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; IBD, inflammatory bowel disease; IQR, interquartile range; MH, mucosal healing; TNF, tumor necrosis factor; UCSD, University of California San Diego.

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absence of ulceration 1 year after the diagnosis was associated with less inflammatory activity ($P = .02$), less corticosteroid use, and a trend toward fewer surgeries ($P = .1$).[6] In another study of a cohort of patients with CD who were starting infliximab, the absence of ulceration or the presence of clear endoscopic improvement after starting infliximab predicted fewer complications and a lower rate of hospitalizations and surgeries.[7] In the ACCENT-I (a Crohn's disease clinical trial evaluating infliximab in a new long-term treatment regimen in patients with Crohn's disease) trial of infliximab as maintenance therapy for CD, a decrease in the rates of CD-related hospitalizations and surgery was observed among patients who achieved MH (defined as no ulceration).[8] In the step-up/top-down trial, MH at 2 years (defined as a simple endoscopic severity of CD score of 0) was predictive of sustained clinical- and steroid-free remission through years 3 and 4.[9] Finally, a decision analysis model that explored treatment strategies for the management of moderate-to-severe CD with infliximab showed that MH as an end point was a cost-effective strategy as compared with a strategy based on clinical symptoms.[10]

Although the idea of MH as a treatment goal or outcome measure increasingly is being considered in patients with CD, at present there is no study that shows the feasibility and effectiveness of using a medical therapy algorithm to reach the goal of MH, a so-called *treat-to-target strategy*. We therefore evaluated the feasibility of treat to target according to endoscopic disease activity to reach MH in clinical practice.

Methods

Study Population

All medical records of consecutive patients referred to the Inflammatory Bowel Disease (IBD) center at the University of California San Diego (UCSD) between January 2011 and December 2012 were reviewed. The International Classification of Diseases, 9th revision, codes were used to identify all patients with a diagnosis of CD or regional enteritis who were referred to UCSD. The diagnosis of CD then was confirmed based on radiologic, endoscopic, and/or histologic evidence. Only patients with CD who had ulcers seen at the initial endoscopic procedure and who had at least 2 consecutive endoscopic procedures performed during the study period were included.

The following demographic and clinical characteristics were abstracted from the electronic medical records of the patients: sex, birth date, age at diagnosis, smoking status, CD phenotype at diagnosis according to the Montreal classification,[11] previous history of surgery and hospitalization, and previous and concurrent treatment for CD.

At the time of each endoscopic procedure, the medical records were reviewed for the type and findings of the procedure, medical therapies being used at the beginning of the study period, any adjustments of medical therapy after endoscopic procedures were performed, and the presence of clinical symptoms at the time of each endoscopic procedure and within 3 to 6 months after each endoscopic procedure. Adjustments of medical therapy after endoscopic procedures were defined as follows: the introduction or switch of immunosuppressives; the introduction, optimization, or switch within the class or out of the class of biologics; or changes in both immunosuppressives and biologics. Patients were defined as having clinical symptoms if they had symptoms of diarrhea and/or abdominal cramping. Endoscopic disease activity was defined by the presence of at least superficial ulcers (including aphthous ulceration) in any segment of the gastrointestinal tract at the time of the endoscopic procedure. To perform sensitivity analyses, we also analyzed separately the presence of deep ulcers and superficial ulcers. Endoscopic lesions were identified by a review of the findings of standardized endoscopy reports, which routinely included color photographs. Of note, the second and subsequent endoscopic assessments were usually a priori planned within 6 months by the treating physician to assess response to therapy (ie, scheduled endoscopic follow-up evaluation to assess for MH).

This study was approved by the UCSD Institutional Review Board.

Statistical Analysis

Quantitative variables were described as medians and percentiles (interquartile range [IQR], 25%–75%). Categoric variables were presented as the number and percentage of the cohort. Two events were defined: (1) MH was defined as the absence of any ulcers in any segment of the gastrointestinal tract during the endoscopic procedure, and (2) endoscopic improvement was defined by the downgrading of deep ulcers to superficial ulcers or the disappearance of superficial ulcers. Patients who underwent surgery during the study period were classified as treatment failures.

The events were analyzed using survival analysis. The cumulative probabilities of MH and endoscopic improvement were estimated using the Kaplan–Meier method. For both, the time to MH or improvement was considered to begin at the date of the first endoscopic assessment and end at the last known follow-up evaluation or at the date of the first procedure during which MH/improvement was observed. To identify factors predictive of each event, we performed a univariate analysis using the log-rank test. We performed univariate analysis to identify the predictors of the outcomes described earlier (characteristics of patients at referral) and the factors associated with outcomes (factors related to management of patients after referral). We then performed a multivariate analysis to identify the independent predictors and factors associated with MH and

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