A Systematic Review of Measurement of Endoscopic Disease Activity and Mucosal Healing in Crohn's Disease: Recommendations for Clinical Trial Design

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Background: Crohn's disease (CD) is a chronic idiopathic inflammatory disorder of the gastrointestinal tract. Recently, mucosal healing has been proposed as a goal of therapy because clinical symptoms are subjective. Evaluative indices that measure endoscopic disease activity are required to define mucosal healing for clinical trials. The primary objective of this systematic review was to assess the existing evaluative indices that measure disease activity in CD and evaluate their role as outcome measures in clinical trials.

Methods: A systematic literature review was performed using MEDLINE (Ovid), EMBASE (Ovid), PubMed, the Cochrane Library (CENTRAL), and DDW abstracts to identify randomized controlled trials and controlled clinical trials that used a relevant evaluative index from inception to February 2013. The data obtained from these trials were reviewed and summarized.

Results: The initial literature searches identified 2300 citations. After duplicates were removed, 1454 studies remained. After application of the apriori inclusion and exclusion criteria, 109 articles were included and 3 were identified with handsearches. In total, 9 evaluative indices for CD were identified and reviewed. The Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score in Crohn's Disease (SES-CD) are indices with the most extensively described operating properties.

Conclusions: Both the endoscopic evaluative instrument selected and the definition chosen for mucosal healing affect the validity of assessing endoscopic disease activity during a clinical trial for CD. Currently, the CDEIS and SES-CD have the most data regarding operating properties; however, further validation is required.

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Key Words: Crohn's disease, Crohn's disease endoscopic index of severity, endoscopic indices, mucosal healing, outcome measures, simple endoscopic score for Crohn's disease, systematic review

Crohn's disease (CD) is a chronic relapsing inflammatory disorder of the gastrointestinal tract in which a dysregulated immune response occurs in genetically susceptible individuals.[1,2] Inflammatory cells accumulate in the bowel wall[3] that cause ulceration of the mucosa, leading to symptoms of abdominal pain and diarrhea. Chronic inflammation results in complications such as strictures and fistulae. Endoscopy has an established role in confirming the diagnosis and extent of CD.[4] Symptoms in patients with CD can result from multiple comorbid processes that are not directly correlated with the pathogenic inflammation process in the gut wall. For this reason, outcome measures in clinical trials in patients with CD are evolving from reliance on symptom-based assessments of disease activity[5] to endoscopic evaluation.[6–8] The evaluative indices used to define endoscopic disease activity can have a substantial impact on the outcomes of clinical trials.

This systematic review assessed the existing evaluative instruments used to assess endoscopic disease activity and mucosal healing in CD. Our objective was to determine the optimal evaluative instrument to measure endoscopic disease activity and assess mucosal healing in clinical trials.

MATERIALS AND METHODS

Search Strategy

A systematic literature review identified the evaluative instruments used to assess endoscopic disease activity in CD. Searches were completed in MEDLINE (Ovid), EMBASE (Ovid), PubMed, the Cochrane Library (CENTRAL), and DDW abstracts

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to identify randomized controlled clinical trials, case-controlled studies, and cohort studies from inception to February 2013 for applicable studies. The following search strategies were used: randomized controlled clinical trials, case-controlled studies, and cohort studies that used an evaluative instrument to assess endoscopic activity of CD were included. Studies that used a CD endoscopic index for assessment of eligibility or an as a clinical endpoint in a controlled study were also included. A complete colonoscopy was necessary, and trials using only sigmoidoscopy were excluded. Case reports, editorials, clinical guidelines, commentaries, letters to the editor, and meeting reports were excluded. Clinical reviews discussing CD endoscopic indices were included for reference review. Abstracts were removed if the full text of the study was subsequently available. Only English language publications were included. Relevant studies identified in the review articles that were not isolated through the literature search were added manually. Citations and abstracts were independently screened by 2 reviewers (R.K. and G.B.). The full-text publications of all potentially eligible articles were retrieved. Study eligibility was assessed independently by 2 reviewers (R.K. and G.B.) and disagreements were resolved by consensus.

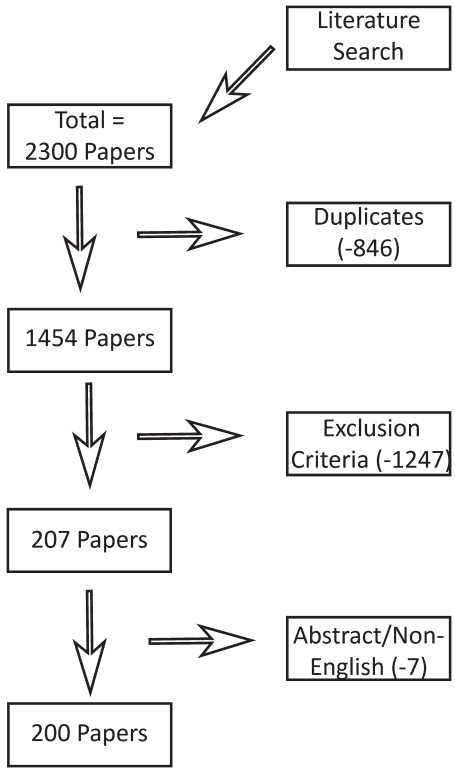

FIGURE 1. Flow chart of the systematic literature search.

RESULTS

The systematic literature search retrieved 2300 citations. After duplicates (847) were excluded, a total of 1453 articles were further assessed. After application of eligibility criteria, 194 articles remained. An additional 88 articles were excluded because the method of endoscopic assessment was unspecified and additional information could not be obtained from the full-text article. Handsearches yielded 6 articles for inclusion. This process resulted in 112 articles for inclusion (Fig. 1). In total, 9 evaluative instruments were identified, of which one specifically assessed postoperative disease (Tables 1 and 2).[9–17]

The following summary focuses on the key evaluative indices used in clinical trials in CD.

First Validated Endoscopic Scoring System for CD: Crohn's Disease Endoscopic Index of Severity

In 1989, Mary and Modigliani[9] developed the Crohn's Disease Endoscopic Index of Severity (CDEIS)[16] in a multiphase study. During the development phase, 2 endoscopists assessed colonoscopies from 75 patients. One endoscopist performed the colonoscopy and the second observed. Data on 9 mucosal lesions, the percentage of segmental surfaces with disease involvement, and the percentage of segmental surfaces with ulcerations were recorded in 5 endoscopic segments (rectum, sigmoid and left colon, transverse colon, right colon, and ileum). A global evaluation of lesion severity (GELS) was determined using a 100-mm visual analog scale. A single value for each procedure was obtained by calculating the average segmental surfaces involved with disease and the average segmental surfaces involved with ulceration. An individual segmental rectocolonic frequency was determined by dividing the number of segments with a lesion by the number of segments explored. Multiple linear regression identified independent variables correlated with the GELS that were subsequently weighted to generate an overall score. The CDEIS[9] assesses the individual segmental rectocolonic frequency deep ulcerations and superficial ulcerations as well as the presence of ulcerated stenosis and nonulcerated stenosis in the 5 segments. These 4 descriptors are combined with the average extent of disease and ulcerated mucosa (Fig. 2). Calculation of the CDEIS is shown in Figure 2. The total score ranges from 0 to 44. Figures 3–5 show representative photos with sample CDEIS calculations. Segments that are not evaluated because of technical difficulties, anastomotic narrowing, or surgery are not accounted for in these calculations.

The operating properties of the CDEIS with respect to agreement, criterion validity, and responsiveness have been partially assessed. Agreement was assessed by determining the intraclass correlation coefficient (ICC) for the CDEIS and GELS based on data from only 2 endoscopists. The ICCs for the CDEIS and GELS were remarkably high (0.96 and 0.86, respectively; $P < 0.001$). However, the 2 endoscopists scored the items while physically present in the same procedure room, which limited the independence of the observations. Nevertheless, a recent study reported that central reading of the CDEIS to assess CD severity, by a group of 4 readers, had "substantial" to "almost perfect" intra- and inter-observer reliability (intraobserver ICC, 0.89;

TABLE 1. Commonly Used Endoscopic Evaluative Instruments for CD Severity

Index	Setting	Description of Scale	Extent of Use	Level of Validation
CDEIS[a] (Mary and Modigliani[9])	Prospective study	Numerical grading system generating a total score (0–44) based on the presence or the absence of the following variables, all of which are recorded in 5 segments: terminal ileum, ascending colon, transverse colon, descending and sigmoid colon, and the rectum	Multiple clinical studies and RCT	Partially validated
		Deep ulceration (0 absent; 12 present); superficial ulceration (0 absent; 6 present); Surface involved by the disease (0–10); ulcerated surface (0–10); ulcerated stenosis (0 absent; 3 present); nonulcerated stenosis (0 absent; 3 present)		
		The percentage of ulcerated surface and surface "affected by Crohn's" are indicated on a 10-cm visual linear analog scale that is ranged from 0 (no lesions or no ulceration at all) to 10 (lesions or ulcerations involving 100% of segmental surface)		
SES-CD[b] (Daperno et al[10])	Prospective study	Numerical grading system generating a total score (0–56) composed of the following variables, all of which are recorded in 5 segments: terminal ileum, right colon, transverse colon, left colon and rectum	Multiple clinical studies and RCT	Partially validated
		Size of ulcers: (0) None; (1) aphthous ulcers (Ø): 0.1–0.5 cm; (2) large ulcers (Ø): 0.5–2 cm); (3) very large ulcers (Ø): >2 cm); Ulcerated surface: (0) None; (1) < 10%; (2) 10%–30%; (3) >30%. Affected surface: (0) Unaffected segment (1) <50%; (2) 50–75%; (3) >75%. Presence of narrowings: (0) None; (1) Single, can be passed; (2) Multiple, can be passed; (3) Cannot be passed	The most recent score, the increasing use	
		The sum of the scores for each variable ranges from 0 to 15, except for stenosis, where it varies between 0 and 11, because 3 represents a stenosis through which an endoscope cannot be passed and therefore can be observed only once		
Postoperative CD recurrence (Rutgeerts et al[11])	Prospective study	Stepwise 5-grade scale: (i0) No lesions in the neoterminal ileum; (i1) <5 aphthous ulcers in the neoterminal ileum; (i2) >5 aphthous lesions in the neoterminal ileum with normal intervening mucosa OR skip areas with larger lesions	Multiple clinical studies and RCT	Partially validated
		OR lesions confined to ileocolonic anastomosis (<1 cm); (i3) diffuse aphthous ileitis with inflamed mucosa; (i4) diffuse inflammation with large ulcers, nodules, and/or strictures		

[a]Calculation formula for CDEIS: CDEIS = sum over all explored segments (score for deep ulceration + score for superficial ulceration + score for surface affected by the disease + score for ulcerated surface) divided by number of segments evaluated plus score for ulcerated or nonulcerated stenosis observed anywhere.
[b]During the score development, the best model obtained was the sum of 4 variables multiplied by 1.007 minus the number of affected segments multiplied by 1.556. However, this formula was simplified as the simple sum of the variable correlated well with CDEIS and CDAI.
Final calculation formula for the SES-CD: SES-CD = sum over all explored segments (score for ulcer size + score for ulcerated surface + score for affected surface + score for stenosis).

95% confidence interval [CI], 0.86–0.93 and interobserver ICC, 0.71; 95% CI, 0.61–0.79).[18]

Criterion validity was examined by measuring the correlation of the CDEIS with the GELS. In an initial set of 75 subjects and a second test set of 103 participants, the correlation was excellent (0.83, $P < 0.001$ and 0.81, $P < 0.001$, respectively). However, these findings may have been biased by the reader's knowledge of clinical information. To test the responsiveness of

TABLE 2. Other Endoscopic Evaluative Instruments Used to Evaluate CD Severity

Index	Setting	Description of Scale	Extent of Use	Level of Validation
Proctoscopy score (Talstad and Gjone[12])	Prospective study	Stepwise 2-grade scale: (1) Slight (2) Severe	Some clinical studies	Not validated
Endoscopy score (part of a simple scoring system) (Myren et al[13])	Retrospective study	Composite score where endoscopy is part of the clinical score: (+12) Normal; (−1) Ulcers; (+2) Stenosis; (−4) Bleeding; (−2) Diffuse; (+16) Patchy Used to differentiate between CD and UC. Overall score: positive favors CD and negative favors UC	Some clinical studies	Not validated
Colonoscopy score (Gomes et al[14])		Numerical grading system generating the total endoscopy score (0–18) based on the presence of 3 variables all of which were recorded in 6 segments (cecal area, the hepatic flexure area, splenic flexure area, descending colon, sigmoid colon, and rectum): (0) Normal (1) Mild inflammation with loss of vascular pattern plus or minus granularity or localized aphthous ulcers (2) Severe inflammation with contact bleeding (3) More severe disease with friability, ulcers, or spontaneous bleeding	Some clinical studies	Not validated
Mayo Score (Schroeder et al[15]	Prospective study	Stepwise 4-grade scale: (0) Normal or inactive disease; (1) Mild disease: erythema, decreased vascular pattern, and mild friability; (2) Moderate disease: marked erythema, absent vascular pattern, friability, and erosions; (3) Severe disease: spontaneous bleeding and ulceration. UC endoscopic scale adapted for evaluation of CD	Multiple clinical studies and RCT	Not validated
GELS (Modigliani and Mary[16])	Prospective study	Linear scale used for a GELS by positioning a cross on a 10-cm linear analog scale (0–10): (0) No endoscopic disease activity; (10) The worst endoscopic disease activity	Many clinical studies and RCT	Partially validated
Froslie endoscopic score (Froslie et al[17])	Prospective study	Stepwise 3-grade scale: (0) Normal; (1) Light erythema or granularity; (2) Granularity, friability and bleeding, with or without the addition of ulceration. Developed for evaluation of both: UC and CD	Some clinical studies	Not validated

the CDEIS, 54 patients with active CD had colonoscopies performed at baseline and 3 to 5 weeks after oral prednisone ($1\ mg \cdot kg^{-1} \cdot d^{-1}$). A high correlation between changes in the CDEIS and GELS was noted ($r = 0.72$, $P < 0.001$). The investigators arbitrarily defined response as a decrease in CDEIS score of >5 points, remission as a CDEIS score of ≤6, and "complete remission" as a score ≤3.[8] However, these designations have not been consistently applied. Elsewhere, CDEIS scores <5, 5–15, and >15 were used to define mild, moderate, and severe disease, respectively.[19] Importantly, none of the conventional metrics of responsiveness, such as the standard effect size or Guyatt responsiveness ratio were defined.[20] No formal analyses have attempted to define a minimal clinically important change in the score. The CDEIS has been used to assess eligibility[8,21] and outcomes[6,8,19,22–48] in clinical trials. The 9 endoscopic parameters that were originally used to develop the CDEIS have also been reported as outcomes.[49] However, this evaluative instrument consists of several subjective components, including the estimate of diseased surface area, which remain incompletely validated.

Simple Endoscopic Score in Crohn's Disease

The inherent complexity of the CDEIS led to the development of the Simple Endoscopic Score in Crohn's Disease (SES-CD).[10] Items from the CDEIS with high interobserver agreement were selected for incorporation into this novel index. The SES-CD[10] grades ulcer size (diameter 0.1–0.5 cm, 0.5–2 cm, or >2 cm), proportion of ulcerated surface (<10%, 10%–30%, or >30), proportion of the surface area affected by any disease lesion (<50%, 50%–75%, or >75%), and stenosis (single, multiple, whether the colonoscopy passes through the narrowing). Each

A CDEIS

	Rectum	Sigmoid & Left Colon	Transverse Colon	Right Colon	Ileum	TOTAL
Deep ulceration If present, score 12 If absent, score 0	⌊⌋	⌊⌋	⌊⌋	⌊⌋	⌊⌋	⌊⌋⌊⌋
Superficial ulceration If present, score 6 If absent, score 0	⌊⌋	⌊⌋	⌊⌋	⌊⌋	⌊⌋	⌊⌋⌊⌋
Surface involved by the disease (measured in cm*)	⌊⌋	⌊⌋	⌊⌋	⌊⌋	⌊⌋	⌊⌋⌊⌋·⌊⌋
Ulcerated surface (measured in cm*)	⌊⌋	⌊⌋	⌊⌋	⌊⌋	⌊⌋	⌊⌋⌊⌋·⌊⌋

TOTAL	⌊⌋⌊⌋·⌊⌋	a
Number *(n)* of segments totally or partially explored (1-5)	⌊⌋	n
Total A divided by n	⌊⌋⌊⌋·⌊⌋	b
Ulcerated Stenosis If present anywhere, score 3 If absent, score 0	⌊⌋	c
Non-Ulcerated Stenosis If present anywhere, score 3 If absent, score 0	⌊⌋	d
TOTAL *b+c+d*	⌊⌋⌊⌋·⌊⌋	

* For partially explored segments and for the ileum, the 10 cm linear scale represents the surface effectively explored.

B SES-CD

	SES CD score			
Variable	0	1	2	3
Presence of ulcers	None	Aphtous ulcers (∅ 0.1–0.5 cm)	Large ulcers (∅ 0.5–2 cm)	Very large ulcers (∅ > 2 cm)
Ulcerated surface	None	< 10%	10–30%	> 30%
Affected surface	Unaffected segment	< 50%	50–75%	> 75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

	Ileum	Right colon	Transverse colon	Left colon	Rectum	SUM
Presence of ulcers						+
Ulcerated surface						+
Affected surface						+
Presence of narrowings						=
					Sum of all variables	TOTAL

FIGURE 2. A, Calculation of the CDEIS (9) B, Definitions of the SES-CD (10).

item is scored from 0 to 3, and a total score is calculated as a sum of all the items in each segment (Fig. 2). Although regression modeling determined the optimal scale to be the sum of the 4 variables multiplied by 1.007−1.556 times the number of segments, this calculation was simplified as the sum of the 4 segments. This simplified index was shown to be highly correlated with the CDEIS (Spearman's r = 0.883) and was similarly poorly correlated with the CDAI (Spearman's r = 0.206) and was, therefore, accepted over the more complex model.[10]

The operating properties of the SES-CD including agreement, validity, and minimally important change have been examined. Agreement for the rederived items was assessed by 2 endoscopists who graded 71 colonoscopies for each of the items in 5 segments. The ICC between observers was 0.9090 for the CDEIS and 0.9815 for the SES-CD. The CDEIS item "superficial ulcers" had a lower level of agreement (0.628–0.767) than "deep ulcers" (0.666–1.0).[10] In a second study, the interobserver agreement was reported as 0.985 (95%CI, 0.939–1.000) and 0.994

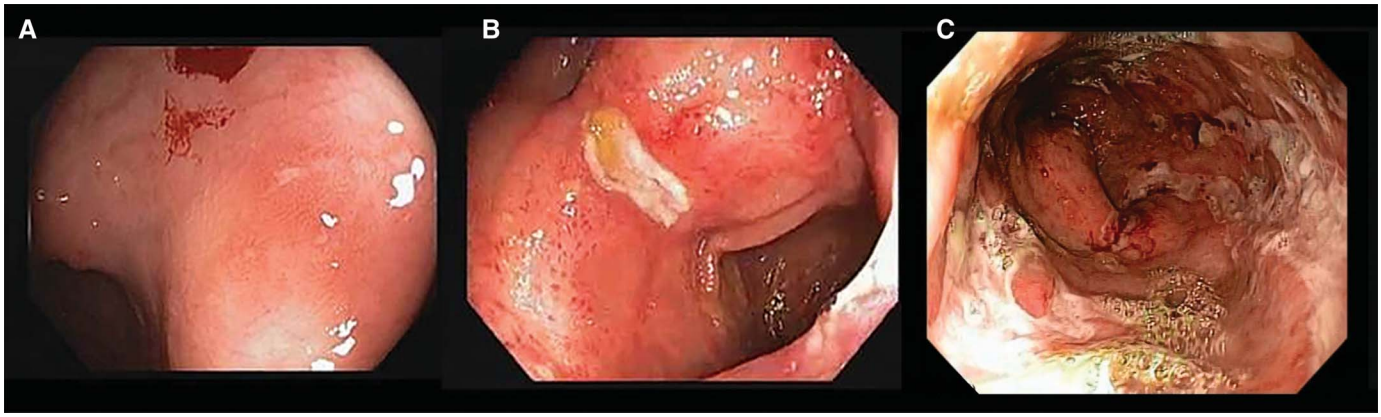

FIGURE 3. Sample endoscopic images representing SES-CD "size of ulcers" variable scoring. From left to right: A, Aphthous ulcers (0.1–0.5 cm). B, Large ulcers (0.5–2.0 cm). C, Very large ulcers (>2.0 cm).

(95%CI, 0.976–1.000) for CDEIS and SES-CD, respectively.[50] However, the agreement of the SES-CD was determined by 2 endoscopists who examined the same procedure simultaneously. Although the endoscopists scored the procedures without communicating, they may have been influenced by each other and knowledge of the patient's condition that may have inflated the estimates of agreement. Recently, central reading of the SES-CD to assess CD severity, factors by a group of 4 readers, had "substantial" to "almost perfect" intra- and inter-observer reliability (intraobserver ICC, 0.91; 95% CI 0.87–0.94 and interobserver ICC, 0.83; 95% CI, 0.75–0.89).[18] During index development, the statistical correlation between the SES-CD and the CDEIS was calculated in 121 additional procedures, using the Pearson product-moment correlation coefficient and the Spearman rank coefficient, which were 0.887 (95% CI, 0.8418–0.9199) and 0.910 (95% CI, 0.8734–0.9364, $P < 0.001$), respectively. Regarding clinical variables, the correlation of the SES-CD was 0.472 with C-reactive protein (CRP), 0.390 for the CDAI, but <0.300 for the IBD Questionnaire, serum albumin, and body-mass index.[10] In a second study, near perfect correlation was again demonstrated between the CDEIS and SES-CD (Spearman's $r = 0.938$, $P < 0.0001$) when both scales were scored by a single endoscopist.[51] The authors report that grading of disease severity (inactive, mild, moderate, and severe) also correlated between the 2 scales ($r = 0.859$, $P < 0.0001$).[51] In a smaller cohort study that evaluated patients with active disease, repeat procedures were performed on average 4 months after the first endoscopy to evaluate responsiveness. The change in these 2 assessments was highly correlated ($r = 0.828$ between ΔCDEIS and ΔSES-CD, $P < 0.001$). Although, the SES-CD correlated with the CDAI ($r = 0.473$) and CRP ($r = 0.525$, both $P < 0.0001$), the correlation with changes in CDAI or CRP ($P > 0.05$) was poor. Similarly, a subgroup analysis from the SONIC trial that examined the role of combination therapy with azathioprine and infliximab compared with monotherapy with either agent, revealed excellent correlation between the change in CDEIS and SES-CD (Pearson's $r = 0.89$, $P < 0.0001$).[52] It is notable that statistical measures of index responsiveness, including the standard effect size, or the Guyatt's responsiveness statistic, were not assessed. Although the minimal clinically important change and the exact relationship between the score and disease activity have not been clearly defined, studies[53,54] have used the following definitions: remission

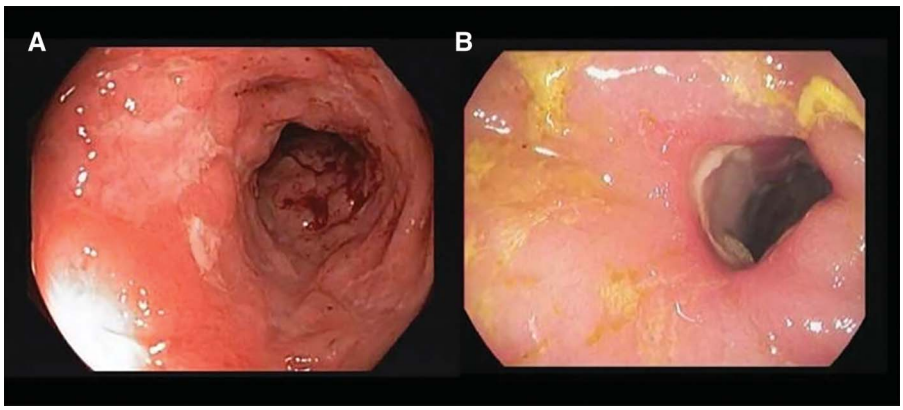

FIGURE 4. Sample endoscopic images representing CDEIS "deep and superficial ulceration" variable scoring. From left to right: A, Superficial ulceration. B, Deep ulceration.

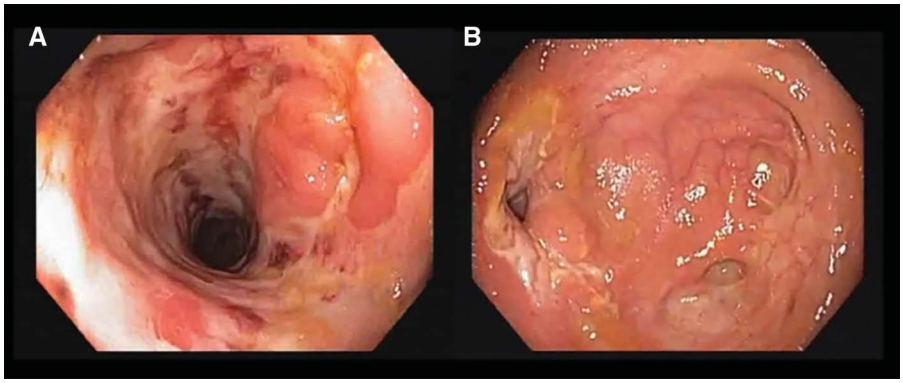

FIGURE 5. Sample endoscopic images representing CDEIS and SES-CD "ulcerated and affected (involved by the disease) surface" and stenosis variables scoring. From left to right: A, Surface involved by the disease (affected): CDEIS (score 10.0) and SES-CD (score 3.0); ulcerated surface: CDEIS (score 9.0) and SES-CD (score 3.0). B, Ulcerated impassable stenosis (narrowing): CDEIS (score 3.0) and SES-CD (score 3.0).

(0–2), mild inflammation (3–6), moderate inflammation (7–16), and severe inflammation (>16). These values have been generated by consensus among authors[54] in distinction to objective data.[53]

Given the high degree of correlation between the CDEIS and the simplicity of its application, the SES-CD has gained popularity for the assessment of eligibility[55] and outcome[36,56–64] in clinical trials. A modified SES-CD that only examines ulcer size and ulcerated surface area has also been reported.[65] The operating properties of this instrument are not defined.

Endoscopic Assessment of Postoperative CD: the Rutgeerts Score

Given that endoscopic recurrence of CD is a near universal phenomenon, development of an evaluative instrument to assess this problem is a research priority. Rutgeerts examined 89 patients with ileal resection for CD.[11] Clinical outcomes in patients with early neoterminal ileal lesions were observed. Although only 20% of patients in this cohort developed symptoms 1 year after surgery, 73% had evidence of endoscopic recurrence. Similarly, the rates of symptomatic and endoscopic recurrence at 3 years were 34% and 85%, respectively. Based on these observations, an endoscopic index for grading postoperative recurrence known as the Rutgeerts score was developed, as shown in Figure 6. Patients with lower scores on this scale had a better prognosis than those with more severe endoscopic lesions. At year 3, endoscopic lesions remained unchanged in 80% of patients with i0 or i1 lesions; however, mucosal disease progression was noted in 92% of patients with i3 or i4 lesions. In a randomized double-blind trial, 80 patients with ileocolonic resection were randomized, within a week of surgery, to 1 year of therapy with ornidazole or placebo for the prevention of disease recurrence. At 1 year, ornidazole significantly reduced both clinical (7.9% compared with 37.5%, $P = 0.0046$) and endoscopic (53.6% compared with 79%, $P = 0.037$) recurrence. In this study, endoscopic disease predicted clinical recurrence.[66] In contrast, the CDAI and serum inflammatory markers, such as the erythrocyte sedimentation rate and CRP have poor correlation with endoscopic recurrence.[67]

In addition, the Rutgeerts score provides prognostic information because 3-year clinical recurrence rates were noted in <5, 15, 40, or 90% of patients with scores of i0-1, i2, i3, or i4 respectively. Although, this scale may predict future disease severity, it remains to be validated as an evaluative instrument. Despite this limitation,[68] it has been used extensively to determine eligibility[69] and efficacy in clinical trials.[66,70–108]

i0: No lesions in the neo-terminal ileum

i1: less than 5 apthous ulcers in the neo-terminal ileum

i2: -greater than 5 apthous lesions in the neo-terminal ileum with normal intervening mucosa

or

-skip areas with larger lesions

or

-lesions confined to ileocolonic anastomosis (less than 1 cm in length)

i3: Diffuse apthous ileitis with inflamed mucosa

i4: Diffuse inflammation with large ulcers, nodules, and/or strictures

FIGURE 6. Rutgeerts postoperative score for assessing endoscopic postoperative recurrence of CD.

Endoscopic Disease Activity Defined by the Presence or Absence of Ulceration

Several trials have used the absence or presence of ulcers on endoscopy as clinical trial endpoints in CD. D'Haens studied the endoscopic healing of CD with azathioprine in a cross-sectional open label study of 20 patients in clinical remission. Endoscopic healing was defined as complete healing (no endoscopic lesions), near complete healing (only aphthous ulcers <5 mm or only erosions if there were previous large or aphthous ulcers), partial healing (large ulcers with a >33% reduction in size), or no healing.[109] The endoscopic substudy of ACCENT I evaluated endoscopic disease activity at weeks 10 and 54 among patients receiving scheduled versus episodic infliximab.[45] Mucosal healing was defined as the absence of mucosal ulceration in all

segments of the colon in patients with previous ulceration in at least 1 colonic segment. The SONIC study assessed the differences in endoscopic appearance in infliximab, azathioprine or combination therapy after 26 weeks of therapy as a secondary endpoint. Mucosal healing was predefined as the absence of ulcerations at week 26 among patients who had ulcerations at baseline.[7] The EXTEND trial was the first randomized placebo-controlled study with endoscopic disease activity in CD as the primary endpoint.[6] Mucosal healing, the primary outcome, was defined as the absence of ulceration at week 12 in patients with moderate-to-severe CD treated with adalimumab. Only 27% of patients in the treatment group attained this outcome, compared with 12% in the placebo group ($P = 0.056$). The major limitation of the presence or absence of ulceration as an outcome measure is that it is relatively insensitive to change and therefore has limited capacity to detect small, but potentially meaningful, treatment effects.

Lack of Correlation Between Symptoms Scores and Endoscopic Disease Activity

The need to consider using an endoscopic index as an outcome measure in clinical trials is highlighted by the lack of correlation between symptom scores and endoscopic disease activity. Jones et al[110] evaluated simultaneous assessment of clinical symptoms through the CDAI; endoscopic inflammation with the SES-CD; serum markers of inflammation, such as CRP and interleukin-6; and the fecal inflammatory markers calprotectin and lactoferrin in 164 patients with CD. No correlation was observed between the CDAI and the SES-CD (Spearman rank correlation coefficient = 0.15). Similarly, the CDAI was not correlated with either the serum CRP and IL-6 concentrations or fecal inflammatory markers. In contrast, these inflammatory markers were highly correlated with endoscopic disease activity ($P < 0.001$ for all comparisons).[110] An analysis of the SONIC trial[7] that compared combination therapy with azathioprine and infliximab to monotherapy with either agent revealed that in 18% of patients who met the key trial inclusion criteria (CDAI >220), objective evidence of endoscopic disease was lacking. A high remission rate was observed for all 3 treatment groups in these patients, and in contrast to the overall trial result, no benefit of combination therapy was demonstrated. Conversely, a greater overall effect size was noted after these patients were excluded from the main analysis.[7]

Endoscopic Scores as Predictive Instruments

The evidence for the predictive validity of endoscopic activity further emphasizes its importance as a clinical trial outcome measure. In the ACCENT I trial of the efficacy of infliximab maintenance therapy in patients with moderate-to-severe CD, the absence of mucosal ulceration at weeks 10 and 54 was associated with a trend toward fewer hospitalizations and surgeries.[45] Froslie and colleagues performed endoscopy in 141 patients with newly diagnosed CD at baseline and within 0.5 and 2 years from diagnosis. In addition, 130 subjects had endoscopy performed at 5 years. Absence of mucosal ulceration at year 1 was associated with reduced steroid use and decreased clinical disease activity ($P = 0.02$) at year 5.[17] An observational analysis of 214 patients with CD with a colonoscopy before the initiation of infliximab and within 12 months of therapy determined that the absence of mucosal lesions was associated with fewer major abdominal surgeries compared with patients with persistent endoscopic inflammation (14.1% compared with 38.4%, respectively, $P < 0.0001$).[111] Similarly, in patients with newly diagnosed CD treated with combination of azathioprine and infliximab or a conventional step-up approach, an SES-CD score (0) 2 years after the initiation of therapy predicted sustained steroid-free remission at 3 and 4 years (odds ratio, 4.352, 95% CI, 1.10–17.220, $P = 0.036$).[56] In contrast, deep mucosal ulceration may predict the need for future colectomy. In a retrospective analysis of 102 patients with active CD, defined as a CDAI >150, colectomy was independently predicted by the presence of deep ulceration in at least 10% of 1 colonic segment (relative risk = 5.43; 95% CI, 2.64–11.18).[112]

Should Mucosal Healing Be Defined by Endoscopic or Histologic Criteria?

Mucosal healing in clinical trials is often defined as the resolution of ulcers on endoscopic assessment. Some large clinical trials[7] have used colonoscopy to define this outcome. However, mucosal healing defined by endoscopy can differ from mucosal healing defined by histologic evaluation of the mucosa.[113,114] The predictive validity of histologic mucosal healing for subsequent clinical outcomes and defining histologic mucosal healing remains to be determined. In contrast, there are now multiple studies showing the predictive validity of an endoscopic definition of mucosal healing for clinical outcomes like risk for future operations and hospitalizations.[7] In addition, an endoscopic definition of mucosal healing correlates with clinical remission in large clinical trials,[7] which provides evidence of criterion validity.

Discussion of Limitations

Although multiple evaluative indices have been used to describe endoscopic severity of CD, only the CDEIS and SES-CD have been used extensively to assess eligibility and response to therapy, and even for these indices, their operating properties such as validity, responsiveness, reliability, and feasibility remain incompletely defined.[115] The CDEIS and, to a lesser extent, the SES-CD rely heavily on estimates of the surface area involved, and the percent of ulceration without a reference standard, which in theory, can lead to inconsistency and variability in the measurement. During the development of the CDEIS and the SES-CD, the endoscopists were not blinded and could have developed an impression of symptom severity during the procedure. The impact of knowledge of symptoms by the endoscopist on the assessment of these evaluative instruments has not yet been determined. The CDEIS investigators did not evaluate the responsiveness of the CDEIS total score or the individual component items with conventional metrics, such as effect size. Understanding the effect size of an evaluative instrument is essential for sample size calculations in clinical trials. Evaluative indices that measure endoscopic disease activity that are highly responsive to change may allow for clinical trials with a smaller sample size. More research is needed in this area.

CONCLUSIONS

The choice and definition of endoscopic evaluative instruments have an important impact on the efficiency and validity of measuring mucosal healing in CD clinical trials. Clinical trials in CD that include endoscopic scores in their primary efficacy endpoints are more likely to predict changes in CD inflammation and long-term outcomes such as surgery. Currently, the CDEIS and SES-CD are promising as endoscopic evaluative indices. Additional validation and potentially optimization of endoscopic evaluative indices for CD and postoperative CD are needed to optimize clinical trial efficiency.

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