Complete Endoscopic Healing Associated With Better Outcomes Than Partial Endoscopic Healing in Patients With Crohn's Disease

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BACKGROUND & AIMS: **Mucosal healing (MH) has been associated with good outcomes of patients with Crohn's disease (CD). It is not clear what levels of endoscopic healing, based on CD endoscopic index score (CDEIS), associate with different courses of disease progression. We assessed long-term outcomes of patients with CD according to different levels of MH.**

METHODS: **We performed a retrospective study of 84 patients with CD and MH who received biologic therapy (80% with infliximab) from 2008 through 2015 at 2 university hospitals in France and compared outcomes of patients with CD endoscopic index scores (CDEISs) of 0 vs CDEISs greater than 0 but less than 4. Patients were followed until treatment failure or through June 2016. The primary outcome measure was treatment failure, defined by the need for biologic optimization, initiation of corticosteroids, or a Harvey-Bradshaw score above 4 associated with change in treatment, CD-related hospitalization, and/or intestinal resection.**

RESULTS: **After a median follow-up time of 4.8 years (interquartile range, 2.1–7.2), 27 patients (32%) had treatment failure and 3 patients (3.6%) underwent an intestinal resection. Rates of treatment failure were 25% in patients with a CDEIS of 0 and 48% in patients with CDEISs greater than 0 but less than 4 ($P = .045$). Median times to treatment failure were 21 months (interquartile range, 5–43 months) in patients with a CDEIS of 0 and 13 months (interquartile range, 3.6–35 months) in patients with CDEISs greater than 0 but less than 4 ($P = .047$). None of the patients with a CEDIS of 0 underwent intestinal resection whereas 11% patients with CDEISs greater than 0 but less than 4 required intestinal resection ($P = .031$). Patients with a CDEIS of 0 also had a significant lower rate of CD-related hospitalizations than patients with CDEISs greater than 0 but less than 4 (3.5% vs 18%; $P = .013$). In multivariate analysis, CDEISs greater than 0 but less than 4 (vs CDEIS = 0) was the only factor associated with treatment failure (hazard ratio, 2.6; 95% CI, 1.2–5.8; $P = .02$).**

CONCLUSIONS: **Complete endoscopic healing (CDEIS = 0) is associated with better long-term outcomes than partial endoscopic healing (CDEIS = 1–4) in patients with CD, as well as fewer surgeries and hospitalizations and an overall decreased risk of treatment failure.**

Keywords: IBD; Biomarker; Response to Treatment; Inflammatory Bowel Diseases.

Crohn's disease (CD) is a chronic and progressive condition that can lead to irreversible bowel damage as strictures, abscesses, fistulas, or intestinal resection.[1,2] With the emergence of anti–tumor necrosis factor agents, more ambitious therapeutic goals have emerged such as mucosal healing (MH). MH has the potential to modify the natural history of CD and has been associated with long-term clinical remission and a

Abbreviations used in this paper: **CD, Crohn's disease; CDEIS, Crohn's Disease Endoscopic Index of Severity; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; MH, mucosal healing; SES-CD, Simplified Endoscopic Score for Crohn's Disease.**

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decreased risk of CD-related hospitalizations and intestinal resections.[3–6] MH is recognized as one of the main therapeutic targets by the International Organization of Chronic Inflammatory Bowel Diseases[7] and the European Crohn Colitis Organization.[8]

Numerous studies looked at the association between MH and disease outcomes. However, the optimal cutoff to change the course of CD is yet to be determined. Baert et al[9] showed that a complete MH (defined as Simplified Endoscopic Score for Crohn's disease [SES-CD] = 0) in patients with early CD was associated with significantly higher steroid-free clinical remission rates as compared with patients with SES-CD between 1 and 9, but no difference was observed in terms of surgery or hospitalization. Schnitzler et al[5] showed that MH improved long-term outcomes, especially a decreased risk of surgery. In this study, the definition of MH was not based on endoscopic score, and the impact on some clinical outcomes such as CD-related hospitalization was not evaluated.

However, no validated definition of MH is currently available. Several endoscopic scores have been proposed to evaluate disease activity, but none of them were designed to evaluate endoscopic remission.[10] No cutoff of Crohn's Disease Endoscopic Index of Severity (CDEIS) or SES-CD has been validated to define MH. Recently, an expert consensus proposed, through a Delphi-like procedure, a CDEIS less than 3 or a SES-CD less than 2 as a definition of MH.[11] However, these definitions were developed for the purpose of regulatory clinical trials to show the anti-inflammatory effect of drugs and not to alter long-term outcome of these patients. Because of the complexity of SES-CD and CDEIS scores, they remain poorly used in routine practice outside of inflammatory bowel disease centers. It is the reason why the absence of ulcerations was proposed as a target in the STRIDE consensus[7] as the absence of ulceration in all examined segments.[12–15]

We therefore conducted a large retrospective multicenter study to investigate the long-term impact of complete endoscopic healing (CDEIS = 0) versus partial endoscopic healing on the outcome of CD patients treated with biologics.

What You Need to Know

Background

It is not clear what level of endoscopic healing associates with Crohn's disease (CD) progression. We assessed long-term outcomes of patients with CD according to different levels of mucosal healing.

Findings

CD endoscopic index scores of 0 (definition of complete mucosal healing) were associated with better long-term outcomes than scores of 1–4, as well as fewer surgeries and hospitalizations and an overall decreased risk of treatment failure.

Implications for patient care

Patients with CD and complete mucosal healing, based on endoscopy scores, require fewer surgeries and hospitalizations and have a significantly reduced risk of treatment failure compared with patients with only partial mucosal healing.

Methods

Study Population

We conducted a retrospective study at Amiens and Nancy University Hospitals in France. Consecutive patients with CD treated with anti–tumor necrosis factor agents (infliximab and adalimumab) or vedolizumab between April 1, 2008 and December 31, 2015 were identified by using existing databases of these 2 centers. The inclusion criteria were (1) adult patients with CD in clinical remission, (2) available colonoscopy before the initiation of biologics, and (3) a second colonoscopy with a CDEIS available and <4. The patients' charts were reviewed for demographic information, disease duration, disease location, and phenotype according to the Montreal classification, previous and concomitant CD-related medications, smoking status, and any history of CD-related surgery. It is noteworthy that in these 2 centers, CDEIS scoring is part of routine practice.

Definitions and Outcome Measures

Two definitions of MH were compared: complete endoscopic healing defined by a CDEIS of 0 (meaning no signs of active inflammation in any colonic segment or in the terminal ileum) and partial MH by a CDEIS >0 and <4. Patients were followed until treatment failure or until last news (June 2016). Treatment failure was defined as an optimization of the ongoing biologic agent (dose increase or interval reduction), introduction of corticosteroids or immunosuppressant, a Harvey-Bradshaw score >4 associated with a therapeutic change (initiation of corticosteroids, immunosuppressants, or optimization of ongoing biologic agent), CD-related hospitalization, and/or CD-related intestinal resection.

Statistics

Quantitative variables were calculated as mean (interval) or median (interquartile range [IQR]), and the qualitative variables were calculated as a percentage. Comparison of the quantitative variables with the normal distribution was performed by the Student t test and the Mann-Whitney test or by the Wilcoxon test for variables with a non-normal distribution. For qualitative variables, a χ^2 test or Fisher exact test was used. Cumulative risk of treatment failure was evaluated by using the Kaplan-Meier method.

A Cox model was used to identify factors associated with risk of treatment failure and with CD-related

hospitalization expressed as hazard ratio (HR) (95% confidence interval [CI]). All variables identified with $P < .10$ were included in a multivariable model. The analysis was performed with SAS software version 9.4 (SAS Institute, Cary, NC). The protocol was approved by the CNIL committee (Comite Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Sante N°T.194 et 1404720).

Results

Baseline Characteristics

Eighty-four patients were included. The characteristics of the study population are detailed in Table 1. The majority of patients had an inflammatory phenotype (n = 55, 65%), an ileocolonic location (n = 51, 61%), and one-third had perianal disease. The treatment initiated was mainly infliximab (80%), associated with immunosuppressants in one-third of patients. The main characteristics of the population were not different between the 2 groups except for disease duration and phenotype. MH was assessed after a median time of 14 months (IQR, 5–24).

Risk of Treatment Failure

After a median duration of follow-up of 4.8 years (IQR, 2.1–7.2), therapeutic failure was observed in 32% of patients (n = 27).

Treatment failure was significantly lower in the CDEIS = 0 group (25%) as compared with the CDEIS >0 and <4 group (48%) ($P = .045$). The risks of treatment failure at 1 year and 3 years were 9% versus 19% ($P = .28$) and 16% versus 37% ($P = .049$), respectively (Figure 1). Median times to treatment failure were 21.5 months (IQR, 4.8–43.3) in the CDEIS = 0 group and 13.5 months (IQR, 3.6–35.3) in the CDEIS >0 and <4 group ($P = .047$) (Figure 2).

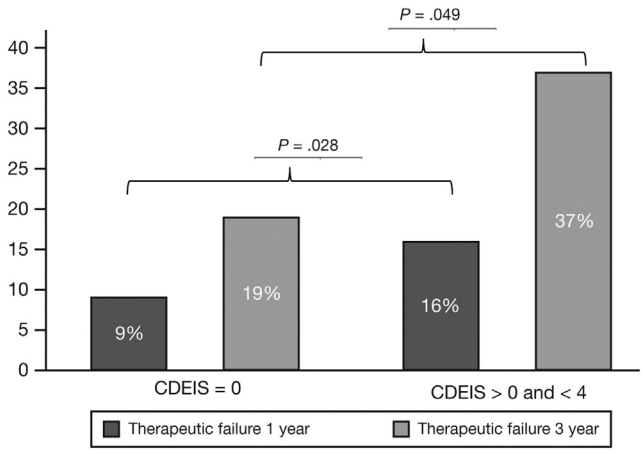

Figure 1. Treatment failure rates at 1 and 3 years according to the 2 definitions of endoscopic healing. CDEIS, Crohn's Disease Endoscopic Index of Severity.

Crohn's Disease–Related Hospitalizations and Surgeries

After a median duration of follow-up of 4.8 years (2.1–7.2), the risk of CD-related hospitalizations was significantly higher in the CDEIS >0 and <4 group

Table 1. Baseline Characteristics of the Study Population

	CDEIS 0	CDEIS >0 and <4	*P* value
Patients (n)	57	27	
Female (n, %)	38 (66.7)	12 (42.9)	.052
Active smokers (n, %)	16 (28.1)	8 (29.6)	.88
Age at diagnosis, *y* (median, IQR)	24.6 (20.27–39.3)	23.4 (19.3–28.9)	.41
Disease duration, *mo* (median, IQR)	10.3 (5.47–17.52)	15.1 (7.4–26.1)	.029
Location (n, %)			
- L1	7 (12.3)	5 (18.5)	.51
- L2	13 (22.8)	6 (22.2)	.95
- L3	37 (34.9)	16 (59.3)	.62
- L4	3 (52.6)	4 (14.8)	.32
Phenotype (n, %)			
- B1	43 (75.4)	16 (59.3)	.13
- B2	1 (1.8)	4 (14.8)	.035
- B3	13 (22.8)	7 (25.9)	.68
Perianal disease (n, %)	19 (33.3)	10 (37)	.75
Extraintestinal manifestations (n, %)	13 (22.8)	2 (7.4)	.13
Previous intestinal resection (n, %)	17 (29.8)	11 (19.3)	.32
Biologics (n, %)			
- Infliximab	46 (80.7)	20 (74.1)	.49
- Adalimumab	9 (15.8)	5 (18.5)	.098
- Vedolizumab	2 (3.5)	2 (7.4)	.59
Immunosuppressants (n, %)	22 (38.6)	10 (37)	.89
Delay of CDEIS assessment, mo (median, IQR)	15 (5–27)	14 (4–20)	.49

CDEIS, Crohn's Disease Endoscopic Index of Severity; IQR, interquartile range.

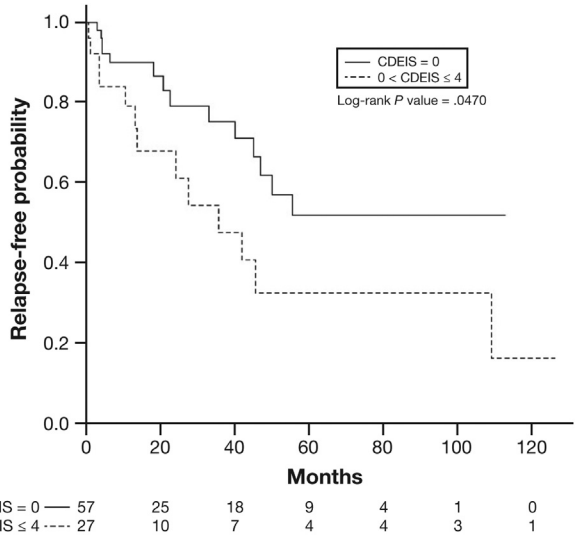

Figure 2. Kaplan-Meier curve of risk of treatment failure according to the 2 definitions of endoscopic healing. CDEIS, Crohn's Disease Endoscopic Index of Severity.

(18.5%) as compared with the CDEIS = 0 group (3.5%) (P = .013). Intestinal resection was also significantly more frequent in the CDEIS >0 and <4 group (11% vs 0%, P = .031). Survival without hospitalization (log-rank P value = .0246) and surgery (likelihood ratio = 0.0082) in the CDEIS = 0 group and in the CDEIS >0 and <4 group are illustrated in Figures 3 and 4.

Factors Associated With Treatment Failure

In both univariate (HR, 2.17; 95% CI, 1.01–4.65; P = .047) and multivariable analyses (HR, 2.61; 95% CI, 1.16–5.88; P = .02), CDEIS >0 and <4 (vs CDEIS = 0) was the only factor associated with treatment failure (Table 2).

In univariate analysis, male gender (HR, 7.13; 95% CI, 1.38–36.8; P = .018), stricturing phenotype (HR, 8.4;

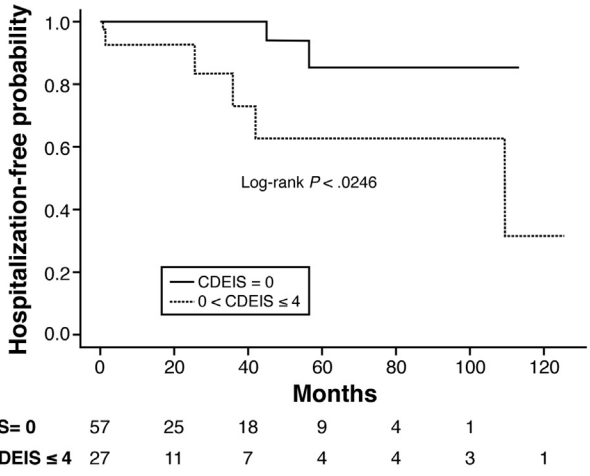

Figure 3. Kaplan-Meier curve of risk of Crohn's disease–related hospitalization according to the 2 definitions of endoscopic healing. CDEIS, Crohn's Disease Endoscopic Index of Severity.

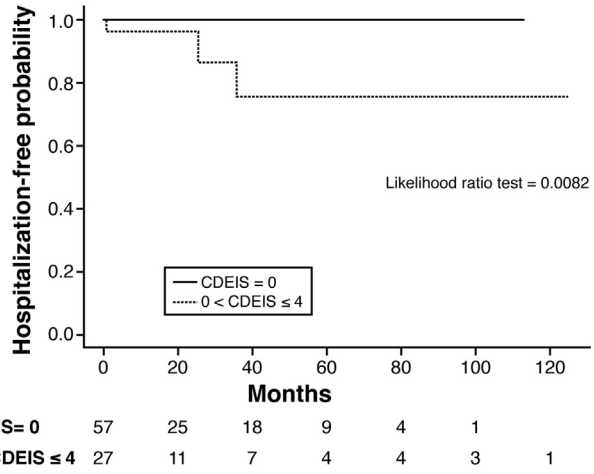

Figure 4. Kaplan-Meier curve of risk of surgery according to the 2 definitions of endoscopic healing. CDEIS, Crohn's Disease Endoscopic Index of Severity.

95% CI, 1.7–41.8; P = .009), and CDEIS >0 and <4 (vs CDEIS = 0) (HR, 6.4; 95% CI, 1.3–32.6; P = .024) were significantly associated to CD-related hospitalization.

Discussion

Several observational studies have shown the importance of MH on the evolution of CD. In these studies, the definitions of MH are extremely variable and heterogeneous. Similarly, although MH is a criterion for judgment of clinical trials during CD as a primary or secondary endpoint, at least 7 different definitions were used in these trials evaluating different biologics.[3,9,16–30] New studies are thus urgently needed to define a clear cutoff value of endoscopic remission that can be used in clinical trials and in clinical practice for a treat-to-target approach. An expert's opinion process recently proposed a CDEIS <3 or a SES-CD <2 to define MH in CD trials.[7]

More recently, it has been demonstrated that a stricter definition of MH, defined by an endoscopic Mayo score of 0 or histologic healing, was associated with a greater long-term clinical benefit in ulcerative colitis patients.[31,32] Here we showed that in CD patients complete endoscopic healing defined by a CDEIS score of 0 is associated with improved long-term outcomes, including CD-related hospitalizations and surgeries.

To our knowledge, only 2 studies have compared different definitions of MH in CD and their impact on long-term outcomes. Baert and al[9] compared the outcomes of patients with complete MH as defined by SES-CD = 0 with patients with SES-CD score between 1 and 9 in early CD. Complete MH (SES-CD = 0) was associated with significantly higher steroid-free remission rates 4 years after therapy began. In a retrospective study from the Leuven group, MH was defined by total disappearance of ulcers, and compared with partial MH defined by a decrease in the CDEIS of 50%, it was not associated with any benefit.[5]

Table 2. Factors Associated With Treatment Failure in Univariate and Multivariate Analysis

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	0.97 (0.94–1.01)	.1793		
Gender	1.23 (0.56–2.71)	.6107		
Smoking status	1.26 (0.55–2.92)	.5854		
Disease duration	1.00 (0.96–1.04)	.9383		
Location				
L1	1			
L2	0.43 (0.09–2.15)	.3069		
L3	0.93 (0.27–3.19)	.9118		
Phenotype				
B1	1			
B2	4.26 (1.33–13.68)	.0149		
B3	0.86 (0.31–2.38)	.7732		
Extraintestinal manifestations	1.29 (0.52–3.22)	.5802		
Previous exposure to steroids	1.79 (0.53–6.01)	.3476		
Previous intestinal resection	0.68 (0.29–1.57)	.3672		
CDEIS <0 and >4 vs 0	2.17 (1.01–4.65]	.0470	2.17 (1.01–4.65)	.0204

CDEIS, Crohn's Disease Endoscopic Index of Severity; HR, hazard ratio.

Through a post hoc analysis of the SONIC trial Ferrante et al[33] looked to the minimal degree of mucosal improvement required to alter midterm outcomes and try to determine the best definition of endoscopic response. MH (defined as the absence of ulcers) and endoscopic response (defined as a decrease from baseline in SES-CD or CDEIS of at least 50%) at week 26 identified patients most likely to be in steroid-free clinical remission at week 50. Recently, the International Organization for the Study of Inflammation Bowel Disease specialists have agreed that the definition of endoscopic response is >50% decrease in CDEIS.[11] This definition is currently used as primary endpoint in numerous clinical trials[34] but should still be validated in an independent, prospective cohort.

Finally, the degree of MH required to achieve a long-term clinical benefit remained unknown. Our findings suggest that we should be more ambitious in clinical practice to change patients' life and disease course by achieving complete endoscopic healing. However, this strategy could be limited by the ability of current drugs to achieve complete MH, which has been observed in about 20% of patients included in the CALM study for example.[30] Obtaining a complete MH would require today a significant need for optimization or change of biologics.

Interestingly, endoscopic remission was associated with less CD-related hospitalizations and surgeries, which are very robust endpoints. Importantly, in multivariate analysis, complete endoscopic healing was the only factor associated with treatment failure. The benefit of complete endoscopic healing was already shown in case of treatment de-escalation. The STORI trial demonstrated that CDEIS of 0 before infliximab withdrawal was associated with a reduced risk of relapse.

Our study has some limitations. First, it is a retrospective study. Second, there was no central reading of endoscopy, and finally, endoscopic follow-up was not standardized. Although CDEIS = 0 objectively reflects a total MH, the definition of partial healing may seem arbitrary. This choice is first justified by the fact that the CDEIS is used in daily practice in our centers. Second, a CDEIS ≤4 is the definition most often used to define MH during clinical trials.[15] Our study also has many strengths. A long-term follow-up of patients was realized through a multicenter study; some robust endpoints such as CD-related hospitalizations and surgeries were evaluated; and CDEIS score before treatment initiation and during follow-up was performed for all included patients.

In conclusion, we showed that patients with CD who achieved complete endoscopic healing defined by CDEIS = 0 had a significantly lower risk of treatment failure including CD-related hospitalizations and surgeries compared with those with partial MH as defined by CDEIS >0 and <4. Similar to ulcerative colitis, a deeper endoscopic healing may be required to change disease course in CD. Before systematically implementing these new findings in our clinical practice, this needs to be investigated in prospective "treat-to-target" intervention trials comparing different targets for MH in CD.

Supplementary Data

Note: to access the supplementary materials accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2019.11.025.

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Conflicts of interest
These authors disclose the following: M.F. has received lecture and consultant fees from AbbVie, Pfizer, MSD, Takeda, Ferring, Janssen, and Boehringer. L.P.B. has received consulting fees from AbbVie, Amgen, Biogaran, Biogen, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Celltrion, Ferring, Forward Pharma, Genentech, H.A.C. Pharma, Hospira, Index Pharmaceuticals, Janssen, Lycera, Merck, Lilly, Mitsubishi, Norgine, Pfizer, Pharmacosmos, Pilège, Samsung Bioepis, Sandoz, Takeda, Therakos, Tillots, UCB Pharma, and Vifor and lecture fees from AbbVie, Ferring, H.A.C. Pharma, Janssen, Merck, Mitsubishi, Norgine, Takeda, Therakos, Tillots, and Vifor. The remaining authors disclose no conflicts.