

CLINICAL—ALIMENTARY TRACT

Mucosal Healing Predicts Sustained Clinical Remission in Patients With Early-Stage Crohn's Disease

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This article has an accompanying continuing medical education activity on page e10. Learning Objective: Upon completion of reading this article, successful learners will be able to interpret the concept of mucosal healing in Crohn's disease, as well as identify patients that would benefit from an endoscopic evaluation and integrate the endoscopic findings as a prognostic marker in the management of Crohn's disease patients.

BACKGROUND & AIMS: Few prospective data are available to support the clinical relevance of mucosal healing in patients with Crohn's disease. This study examined whether complete healing, determined by endoscopy, predicts a better outcome in Crohn's disease. **METHODS:** One-hundred thirty-three newly diagnosed and treatment-naïve Crohn's disease patients were given either a combination of immunosuppressive therapy (azathioprine) and 3 infusions of infliximab or treatment with conventional corticosteroids. Patients given azathioprine were given repeated doses of infliximab for relapses, patients given corticosteroids were given azathioprine in cases of corticosteroid dependency and infliximab only if azathioprine failed. A representative subset of 49 patients from the initially randomized cohort underwent ileocolonoscopy after 2 years of therapy. Correlation analysis was performed between different clinical parameters including endoscopic activity (Simple Endoscopic Score) and clinical outcome 2 years after this endoscopic examination. Data were available from 46 patients 3 and 4 years after therapy began. **RESULTS:** Complete mucosal healing, defined as a simple endoscopic score of 0 after 2 years of therapy, was the only factor that predicted sustained, steroid-free remission 3 and 4 years after therapy was initiated; it was observed in 17 of 24 patients (70.8%) vs 6 of 22 patients with lesions detected by endoscopy (27.3%, Simple Endoscopic Score >0) ($P = .036$; odds ratio = 4.352; 95% confidence interval, 1.10–17.220). Fifteen of 17 patients with mucosal healing at year 2 maintained in remission without further infliximab infusions during years 3 and 4 ($P = .032$; odds ratio = 4.883; 95% confidence interval, 1.144–20.844). **CONCLUSIONS: Complete mucosal healing in patients with early-stage Crohn's disease is**

associated with significantly higher steroid-free remission rates 4 years after therapy began.

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Crohn's disease (CD) is a chronic relapsing inflammatory condition that primarily affects young individuals, often leading to significant impairment of quality of life. At present, potent medical therapies, including biologics and immunosuppressives, are often reserved as last-resort treatments for patients refractory to conventional management. Due to a lack of useful prognostic markers, current disease management remains largely clinically guided. However, symptoms usually correlate poorly with disease activity and better prognostic markers are needed.

In our recently published study, we found that combination immunosuppressive therapy with infliximab and azathioprine led to significantly higher mucosal healing rates compared with conventional management (CM) in patients with newly diagnosed CD, despite comparable clinical steroid-free remission rates after 2 years of treatment.¹ To date, the clinical benefit of achieving complete mucosal healing has not yet been demonstrated in a prospective study. Recent data from a Norwegian popu-

Abbreviations used in this paper: CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CIS, combined immunosuppressive treatment; CM, conventional management; SES-CD, Simple Endoscopic Score; TNF, tumor necrosis factor.

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lation-based cohort, before the era of biologics, suggested that mucosal healing is predictive of reduced disease activity and decreased need for active treatment and surgery.²

In the current study, we prospectively followed a cohort of newly diagnosed Crohn's patients for 2 years after ileocolonoscopy, focusing on the differences in clinical outcomes of patients who achieved complete mucosal healing compared with those who had persistent endoscopic activity. We hypothesized that patients achieving complete mucosal healing had superior long-term clinical outcomes.

Methods

This was a prospective, 2-year follow-up of a previously published study in a cohort of CD patients.¹ In summary, 133 newly diagnosed and treatment-naïve CD patients were randomized at 18 centers to receive either combined immunosuppressive treatment (CIS) with azathioprine (2.5 mg/kg) and 3 infusions of infliximab 5 mg/kg or CM with initial corticosteroid therapy. In the CIS group, patients with a relapse were given repeated infliximab infusions as needed. In the CM group, azathioprine was given on flare-up after a second course of corticosteroids or when steroids could not be tapered according to a fixed scheme. Infliximab was given only after failure of 3 months of azathioprine. The initial study started in May 2001 when the first patient was randomized, and continued through January 2004 when the last patient had reached year 2.¹

Eight of the 18 centers participated in an endoscopic substudy. All 49 patients (26 CIS, 23 CM) at these centers who were treated per protocol underwent ileocolonoscopy at year 2. Endoscopic activity was scored using the Simple Endoscopic Score (SES-CD).³ Complete mucosal healing was defined as a SES-CD of 0, meaning no signs of active inflammation in any colonic segment or in the terminal ileum.

This study reports on the extended follow-up of these 49 patients through years 3 and 4 (the 2 years following endoscopic evaluation). All patients followed strict treatment guidelines until the last patient had reached year 2 and the initial trial had formally ended. Thereafter, patients continued with the same treatment or were treated according to currently accepted guidelines at the discretion of the investigator. After January 2006, patients in need of repeated infliximab infusions were switched from episodic ("on demand") to maintenance infliximab treatment every 8 weeks according to revised guidelines.⁴ Detailed clinical data including treatment were collected for all patients.

All patients were seen for outpatient clinic visits on a routine basis every 3 months until the last patient in the study had reached year 2. At each of these 3 monthly visits, a Crohn's Disease Activity Index (CDAI) was calculated. Median follow-up for these measurements in the

current study was 19.2 months. After this period, patients were evaluated clinically using the Harvey Bradshaw Index and physical examination. In addition, investigators completed follow-up questionnaires for each patient at the end of year 3 and year 4. The questionnaire was comprised of clinical parameters regarding disease status (overall disease status, flares, fistulas, endoscopy, x-rays), disease-related medications, adverse events, comorbidities, and disease-related hospitalizations. Overall disease status was summarized as follows: "clinical remission" was defined as a symptom-free state throughout the entire 2-year follow-up period, "mildly active," "moderately active," or "severely active," defined per average CDAI at different outpatient clinic visits and/or as determined by the principal investigators. The main endpoint of this study was stable remission and no use of corticosteroids during the entire 2-year follow-up period. For remission, the classical CDAI criterion (<150) was used or a Harvey Bradshaw Index <3. A flare was defined as any change in the disease course that required an unscheduled visit or admission to the hospital and or a change in medication. Patients needing repeated infliximab infusion because of a flare were not considered in remission. In contrast, patients who were switched from an on-demand schedule to maintenance infliximab every 8 weeks were counted separately. Therefore, an additional endpoint, "in remission off steroids and no anti-tumor necrosis factor (TNF) therapy" was used to split up remissions with or without infliximab.

Informed consent was obtained from all patients to extend the initial study. This follow-up was approved by the central and local institutional review boards at each participating center.

Statistical Analysis

Data for clinical remission were combined for years 3 and 4 (the 2 years following the endoscopic evaluation). Mucosal healing was used as a binary variable (healing or no healing) as was done in other studies.^{1,2} A Fisher's exact 2-sided test was used to compare the mucosal healing group with the nonmucosal healing group. Statistical Program for the Social Sciences 17.0 (SPSS Inc, Chicago IL) was used for statistical analysis. An α level of 5% was considered as threshold for significance. In addition, multiple logistic regression analysis was performed with all variables and showed a trend toward significance in univariate analysis ($P < .1$) included in the model.

Results

Data Collection

The initial trial included 129 evaluable patients of a total of 133 patients randomized in 18 centers. Eight

centers agreed to participate in an endoscopic substudy. All 49 patients from these 8 centers underwent an ileocolonoscopy 2 years after enrollment in the initial trial. These patients had similar baseline characteristics compared with the entire main study sample. At the time of follow-up analysis, year-4 data were available in 46 (94%) of 49 patients (25 CIS; 21 CM). Three patients were lost to follow-up. Complete mucosal healing (SES-CD = 0) was observed in 24 patients (52%; 18 CIS; 6 CM) and endoscopic activity (SES-CD >0) was observed in 22 patients (48%; 7 CIS; 15 CM). The 2-year SES-CD did not correlate with the CDAI or with any other clinical parameters at inclusion in the initial study.¹

Remission Rates

Several potential predictive factors both at diagnosis and at year 2 were studied. Age, location of CD, smoking history, CDAI, hematocrit, and C-reactive protein levels at diagnosis were not significantly correlated with prognosis. Remission status (or CDAI), C-reactive protein, hematocrit, and previous infliximab use at year 2 did not correlate with clinical outcomes either (Tables 1 and 2). Although a higher proportion of patients initially

Table 1. Predictive Factors at Diagnosis for Remission During Year 3 and Year 4 (Univariate Analysis)

Predictive factors	n	Remission	Remission off steroids	Remission off steroids, no anti-TNF
Age (y) at diagnosis	46	26	23	19
<25	23	11	10	7
25–35	9	5	4	4
>35	14	10	9	8
P value		.37	.439	.272
Location at diagnosis	46	26	23	19
Colon only	10	4	4	4
Ileocolitis	27	15	13	10
Small bowel only	9	7	6	5
P value		.250	.487	.618
Smoking	46	26	23	19
Current	12	7	7	7
Former	16	11	9	6
Never	18	8	7	6
P value		.357	.479	.367
CDAI at inclusion	46	26	23	19
Mild	15	8	7	6
Moderate	16	11	9	8
Severe	15	7	7	5
P value		.443	.826	.637
C-reactive protein	18	18	14	11
<5 mg/L	9	9	6	6
>5 mg/L	9	9	8	5
P value		1	.58	1
Hematocrit	20	20	19	16
<35%	8	8	8	8
>35%	12	12	11	8
P value		1	1	.12

CDAI, Crohn's Disease Activity Index; CIS, Combined Immunosuppressive Treatment; CM, conventional management; IFX, infliximab; SES-CD, Simple Endoscopic Score; TNF, tumor necrosis factor.

Table 2. Predictive Factors at Year 2 for Remission During Year 3 and Year 4 (Univariate Analysis)

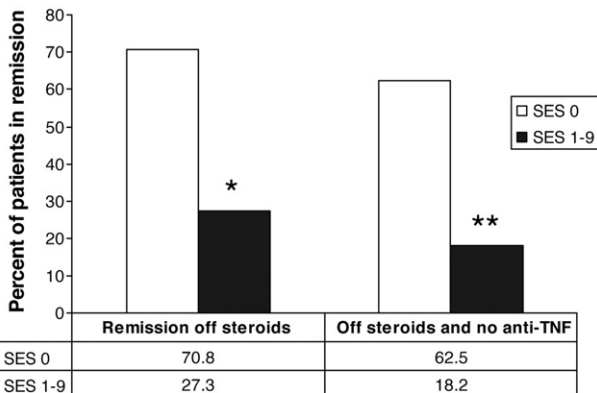
Predictive factors at Year 2	n	Remission	Remission off steroids	Remission off steroids, no anti-TNF
Previous medication	46	26	23	19
CM	21	9	6	4
CIS	25	17	17	15
P value		.14	.017	.0071
Endoscopic healing	46	26	23	19
SES-CD 0	24	17	17	15
SES-CD 1–9	22	9	6	4
P value		.073	.0072	.0031
CDAI at year 2	42	25	22	19
<150	31	20	18	15
150–250	4	1	1	1
>250	7	4	3	3
P value		.314	.395	.670
C-reactive protein	42	25	22	19
<5 mg/L	30	18	17	15
>5 mg/L	12	7	5	4
P value		1	.499	.494
Hematocrit	41	24	21	18
<35%		0	0	0
>35%		24	21	18
Previous IFX therapy	44	24	21	17
Yes	33	19	18	14
No	11	5	3	3
P value		.51	.168	.485

CDAI, Crohn's Disease Activity Index; CIS, combined immunosuppressive treatment; CM, conventional management; IFX, infliximab; SES-CD, Simple Endoscopic Score; TNF, tumor necrosis factor.

Bold type indicates statistical significant factors.

treated with combined immunosuppression treatment were in remission than of those treated with CM, multiple logistics regression analysis revealed that endoscopic healing was the only significant factor.

Stable, steroid-free remission was observed through years 3 and 4 in 17 of 24 (70.8%) patients achieving complete mucosal healing (SES-CD of 0) at year 2, compared with only 6 (27.3%) of 22 patients with endoscopic activity (SES-CD 1-9) ($P = .036$; odds ratio = 4.352; 95% confidence interval, 1.10–17.220). Steroid-free remission without anti-TNF therapy was observed in 15 of 24 (62.5%) patients in the SES-CD = 0 group, but in only 4 of 22 (18.2%) patients in the SES-CD = 1 to 9 group ($P = .032$; odds ratio = 4.883; 95% confidence interval, 1.144–20.844) (Figure 1). The same analysis was repeated with only 31 of 42 patients in remission based on CDAI (CDAI available in 42 of 46 patients) at year 2. Only 16 of 31 patients (52%) in clinical remission had mucosal healing. Thirteen of these 16 patients (81.2%) remained in clinical remission off steroids compared to only 5 of 15 (33.3%) of patients with mucosal lesions ($P = .066$). In addition, 8 of 11 (73%) patients not in clinical remission did have mucosal healing.



Multiple logistic regression analysis:
 * $P=.036$;OR 4.352 (95% CI 1.10-17.220)
 ** $P=.032$;OR 4.883 (95% CI 1.144-20.844)

Figure 1. Remission status during year 3 and year 4 according to Simple Endoscopic Score (SES-CD) at year 2.

Adverse Events, Comorbidities, and Hospitalizations

One patient (4.2%) with complete mucosal healing reported a persistent perianal fistula, and 5 of 22 (22.7%) patients with a SES-CD 1 to 9 reported a new (n = 2) or persistent actively (n = 3) draining perianal fistula during follow up ($P = .089$).

A total of 23 flares in 14 patients were observed during the study. Six flares occurred in 4 of the 24 (16.7%) patients with mucosal healing compared to 17 flares in 10 of the 22 (45.5%) patients in the group with endoscopic activity. The number of flares per patient is shown in Figure 2.

No major resective bowel surgery for CD was performed in either group. Minor Crohn’s surgery, including incision and drainage of abscesses, was performed in 1 patient in the SES-CD 0 group and in 3 patients in the SES-CD >0 group. One patient in the mucosal healing group was hospitalized for a flare of CD, although there were no hospitalizations in the endoscopic activity group.

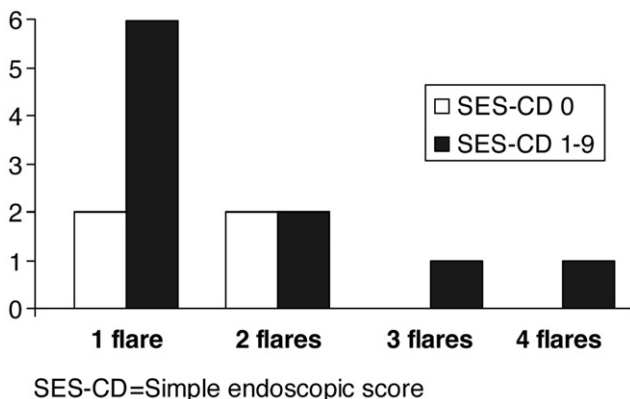


Figure 2. The number of Crohn’s disease flares per patient during years 3 and 4 according to mucosal healing status.

Table 3. Predictive Factors Clinical Outcome Data During Year 3 and Year 4 According to SES-CD Obtained at Year 2

Years 3–4 data	SES-CD 0 (n = 24)		SES-CD 1–9 (n = 22)		P value
	n	%	n	%	
Disease activity status					
Remission	17	70.83	9	40.91	.223
Mildly active	3	12.50	6	27.27	
Moderately active	3	12.50	6	27.27	
Severely active	1	4.17	1	4.55	
Adverse events					
New or active draining fistula	1	4.17	5	22.73	.0089
CD minor surgery (incision/drainage)	1	4.17	3	13.645	.226
CD major surgery (resection)	0	0	0	0	1
CD hospitalization	1	4.17	0	0	.522

CD, Crohn’s disease; SES-CD, Simple Endoscopic Score. Bold type indicates statistical significant factors.

No significant differences in the number of other minor and serious adverse events were noted between the 2 groups (Table 3).

Medication Use Beyond Year 2

At the beginning of this follow-up study, there were no significant differences in medication use between the CM and the CIS group. All but 3 patients remained on immunosuppressives throughout the study. These 3 patients were in the mucosal healing group (SES-CD 0) and maintained stable clinical remission despite discontinuation of all medical therapies. No patients in the endoscopic activity group (SES-CD 1–9) maintained stable clinical remission without medication. During the study anti-TNF therapy was used in 8 (33%; 7 infliximab, 1 adalimumab) of the 24 patients in the SES-CD 0 compared to 14 (64%; 12 infliximab, 2 adalimumab) of 22 patients in the SES-CD 1 to 9 group. All medication use, both maintenance and add-on medication is summarized in Table 4.

Table 4. All Crohn’s Medication Used During Year 3 and Year 4 According to SES-CD at Year 2

Medication use during years 3–4	SES-CD 0 (n = 24)		SES-CD 1–9 (n = 22)		P value
	n	%	n	%	
Corticosteroids (any)	3	12.50	5	22.73	.204
Azathioprine or methotrexate	21	87.50	22	100	.133
Infliximab	7	29.17	12	54.55	.054
Other anti-TNF therapy	1	4.17	2	9.09	.365
No therapy	3	12.50	0	0	.133

SES-CD, Simple Endoscopic Score; TNF, tumor necrosis factor.

Discussion

This is the first prospective study examining the clinical predictive value of mucosal healing in patients with CD in the era of the biologics and immunosuppressants. This study is an extended follow-up study of our earlier reported study comparing combined immunosuppressive treatment to conventional management (The Step Up Versus Top Down Study) in treatment-naïve early CD patients.¹ We hypothesized that patients achieving mucosal healing at the end of 2 years would have better outcomes in the subsequent 2 years (years 3–4). We observed a clear statistical difference in remission rates for the patients with complete mucosal healing as assessed by endoscopy 2 years after initiation of their first therapy for CD. In addition, only 1 of 24 patients with mucosal healing had a persistently active draining fistula. In contrast to 5 of 22 patients with endoscopic activity that developed a new fistula or had persistent fistula activity. Finally, more flares were seen in the group with endoscopic activity during the 2-year follow-up. No difference was observed in the number of hospitalizations or major surgery in the 2 groups. This is probably due to the limited sample size and/or duration of follow-up. None of the other markers analyzed both at diagnosis and at year 2 was predictive for clinical remission in the next 2 years. Mucosal healing was a predictive marker irrespective of the CDAI. CDAI at year 2 did not correlate with mucosal healing.

Two decades ago, Rutgeerts et al reported on the value of an endoscopic score to predict recurrent CD after a "curative resection."^{5,6} Similarly, there is now a growing body of evidence that endoscopic appearance may also be of predictive value in "established disease." Frøslie et al reported that mucosal healing at 1 year predicted a decreased need for steroid therapy and less anal fistula activity in a Norwegian population-based Inflammatory Bowel Disease cohort.² This study is a cohort study of a population treated with corticosteroids and mesalamine, before immunosuppressants and biologic therapy were widely used in Norway and therefore probably reflects the natural history of the disease.

With the advent of immunosuppressants, and especially anti-TNF therapy, mucosal healing rates increased considerably.^{7,8} Emerging evidence suggests that these therapies will not only reduce disease activity but also long-term complication rates. Following the A Crohn's Disease Clinical Study Evaluating Infliximab in a New Long Term Treatment Regimen (ACCENT-1) trial, patients with complete or near-complete endoscopic healing at week 54 were in remission for a median of 19 to 20 weeks following the final endoscopy, compared to only 4 weeks in patients without signs of healing.⁹ In the same trial, patients with absence of ulcers had fewer operations and hospitalizations than patients without mucosal healing.¹⁰ A limitation of our current study is that medical treatment was no longer standardized after termination

of the initial study. However, median follow-up of our patients in the formal trial beyond their 2-year endoscopy was 19.2 months. During this period, treatments were comparable among both groups with almost uniform maintenance therapy with azathioprine. Better outcomes in the mucosal healing group cannot be explained by the difference in medication use because use of infliximab was lower in the mucosal healing group.

When we stratified patients with and without healing based upon their initial disease management (CM or CIS), we found no differences in clinical outcomes (data not shown), confirming that achieving mucosal healing is the sole determining predicting factor and not the treatment.

All Crohn's medication could be stopped without flare of the disease for 2 years in 3 patients in the mucosal healing group. These results are in agreement with recent findings of an early rheumatoid arthritis study in which 19% of patients treated with a combination of infliximab and methotrexate from the start were in remission and could stop all medication at 5 years' follow-up.¹¹

Mounting evidence on the efficacy and relative safety of biologics and immunosuppressants both as monotherapy and in combination are challenging the current paradigm of "step-up" therapy guided by clinical success or failure rather than by predictive markers.¹² Recent data from the Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) trial have confirmed the superiority of combined immunosuppression achieving mucosal healing in early CD.¹³ Although current use of biologics has changed to maintenance therapy, our data, systematically and prospectively collected in a well-defined cohort of treatment-naïve Crohn's patients, support the strategy of aggressive induction therapy, including biologic therapy (so-called "top down") in early CD, with possibly subsequent step-down therapy when complete mucosal healing is reached.

Future research should continue to explore the value of mucosal healing. Stool markers, including calprotectin and lactoferrin, have been suggested as reliable noninvasive substitutes for endoscopy.¹⁴ Others have suggested that transmural healing might be a superior endpoint, although correlations between mucosal and transmural healing have not yet been studied. In the future, novel imaging methods, such as computed tomography or magnetic resonance imaging enterography/enteroclysis may prove to be superior. Clearly there is a compelling need to move beyond conventional management in Crohn's therapy.

This prospective clinical study provides evidence that complete mucosal healing can lead to significantly higher steroid-free remission rates through 2 years in patients with CD. Given that we have previously shown that mucosal healing rates in the CIS group were higher, these data further support that a top-down approach in early CD can alter its disease course.

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Conflicts of interest

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