Combined Endoscopic and Radiologic Healing Is Associated With a Better Prognosis Than Endoscopic Healing Only in Patients With Crohn's Disease Receiving Anti-TNF Therapy

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INTRODUCTION: **Although endoscopic healing (EH) is recommended as the therapeutic goal in patients with Crohn's disease (CD), combined EH and radiologic healing (RH) could be a more ideal therapeutic goal considering the transmural nature of CD. We compared the prognosis of patients with CD who achieved EH, RH, both EH and RH (deep healing; DH), or no healing under treatment with anti-tumor necrosis factor (TNF) agents.**

METHODS: **We analyzed 392 patients with CD who received anti-TNF treatment for more than 1 year and evaluated with CT enterography or magnetic resonance enterography together with colonoscopy within 3 months between July 2017 and December 2018. Major outcomes (anti-TNF dose intensification, switch to other biologics, CD-related bowel resection, and hospitalization) were compared according to the EH and RH status.**

RESULTS: **During the follow-up (median 18 months; interquartile range, 15–21), the DH group showed a better rate of major outcome-free survival compared with other groups ($P < 0.001$). In multivariable analysis, elevated C-reactive protein (adjusted hazard ratio [aHR], 2.166; 95% confidence interval [CI], 1.508–3.110; $P < 0.001$), EH-only (aHR, 3.903; 95% CI, 1.635–9.315; $P = 0.002$), RH-only (aHR, 3.843; 95% CI, 1.545–9.558; $P = 0.004$), and no healing (aHR, 8.844; 95% CI, 4.268–18.323; $P < 0.001$) were associated with increased risks of major outcomes.**

DISCUSSION: **Patients with CD who achieved DH under anti-TNF therapy showed a better prognosis compared with those who only achieved EH. The possibility of DH being used as a new therapeutic target for patients with CD should be investigated in further studies.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A738, http://links.lww.com/CTG/A739

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease that affects the entire gastrointestinal tract from the mouth to the anus (1). CD has been a common disease in Europe and North America, but its incidence is also increasing in Asia and is becoming a global health problem (2–4). Although CD is a progressive disease with waxing and waning of symptoms, symptom-based scoring systems, such as Crohn's disease activity index (CDAI) and Harvey-Bradshaw index, have been shown to be poorly correlated with actual inflammation assessed by objective tools, such as blood test, endoscopy, and radiology (5–10).

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Therefore, according to the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) consensus, the recommended therapeutic target of CD is achieving patient-reported outcome remissions defined as the resolution of abdominal pain and diarrhea/altered bowel habit together with endoscopic remission or the resolution of findings of inflammation on cross-sectional imaging in those who cannot be adequately assessed with ileocolonoscopy, not setting radiologic transmural healing as a target (8). The updated STRIDE-II consensus also recommended the cross-sectional imaging as an adjunctive measure, not as a formal treatment target (9).

However, although the STRIDE and STRIDE-II consensus recommended endoscopic healing (EH) as a therapeutic target, EH alone might not be sufficient as a therapeutic target because CD is a transmural disease (1,8,9). Recently, the concept of radiologic healing (RH), evaluated through imaging modalities, such as computed tomography enterography (CTE), magnetic resonance enterography (MRE), and intestinal ultrasound (IUS), has been proposed as a therapeutic target for patients with CD (11–14). Moreover, several studies have reported that patients with RH have a better prognosis than those without (15–21). Based on those observations, the therapeutic target of CD could be upgraded to achieving RH in addition to EH. However, the prognostic differences in patients with CD according to the achievement of EH, RH, or both have not been sufficiently studied. Therefore, we compared the prognosis of patients with CD under anti-tumor necrosis factor (TNF) treatment by classifying them into 4 groups according to the achievement of EH and RH.

METHODS

Study population

We retrospectively analyzed the data of patients with CD treated with anti-TNF agents at Asan Medical Center, a tertiary hospital in Seoul, South Korea. The diagnosis of CD was based on the conventional clinical, radiologic, endoscopic, and histopathologic findings (22,23). Of them, we included patients who underwent an endoscopic evaluation, radiologic evaluation, and blood tests (e.g., complete blood cell count, serum chemistry, and C-reactive protein [CRP]) within the same period (within 3-month interval) between July 2017 and December 2018; the observation period was started after ileocolonoscopy or CTE/MRE, whichever was conducted later. We excluded patients (i) who had been treated with anti-TNF therapy for less than 1 year before the endoscopic evaluation or radiologic evaluation, (ii) in whom the delay between endoscopic evaluation and radiologic evaluation was longer than 3 months, and (iii) whose follow-up observation period was less than 1 year. Clinical information was extracted from the prospectively managed inflammatory bowel disease (IBD) registry (24) and the electronic medical records of Asan Medical Center. We collected data on sex, birth date, date of CD diagnosis, date of anti-TNF therapy commencement, smoking status, family history of IBD, location and behavior of CD defined by the Montreal classification, and history of intestinal resection (25).

Endoscopic and radiologic evaluation

Before the initiation of anti-TNF therapy, all patients with CD were evaluated using the CDAI score, biochemistry, including CRP, ileocolonoscopy, and imaging with CTE or MRE (24). The details of anti-TNF therapy and evaluation before every infusion of infliximab or prescription of adalimumab have been described previously (24). At 1 year after starting anti-TNF therapy, ileocolonoscopy, imaging (CTE or MRE), and laboratory evaluation, including biochemistry, were performed to evaluate the patients' response to anti-TNF therapy even if they were in clinical remission (i.e., CDAI <150) (24). Even before 1 year, ileocolonoscopy, imaging (CTE or MRE), and biochemical tests were performed if patients did not show clinical and/or biochemical responses to treatment or showed clinical flare (24). After 1 year, ileocolonoscopy and imaging (CTE or MRE) were performed every 1–3 years depending on the patients' disease status (24).

During ileocolonoscopy, images of all abnormal lesions together with the images of the terminal ileum and each colonic segment were captured and stored in a image archiving and communication system of Asan Medical Center. EH was defined as no visible ulcer or inflammation associated with CD in the colon and the small bowel (8,24,26,27). All endoscopic images of the study patients were independently reviewed by 2 board-certified endoscopists (B.D.Y. and E.H.O.) who were blinded to the RH status of the patients. In case of disagreement on EH, the endoscopists reached an agreement through a thorough discussion.

For radiologic evaluation, CTE or MRE was performed. To allow proper luminal distension, all patients were given 1,200–1,500 mL of polyethylene glycol or sorbitol solution continuously for more than 30–40 minutes in small aliquots before CTE or MRE. For MRE, gadolinium contrast (0.2 mL/kg body weight of gadoterate meglumine [Dotarem; Guerbet, Villepinte, France]) was administered intravenously for contrast-enhanced T1-weighted sequences (24). CTE was performed in 272 patients and MRE in 120 patients. RH was defined as the absence of mural or perienteric findings of bowel inflammation: normal mural thickness (<3 mm), absence of mural hyperenhancement, normal mural signal, absence of perienteric infiltration, absence of newly developed stricturing or penetrating complications, and absence of worsening preexisting structuring or penetrating complications (16,28–30). All radiologic images were reviewed and interpreted by a board-certified gastrointestinal radiologist (S.H.P.) with experience in evaluating the CTE and MRE images of patients with CD, who were blinded to the endoscopic and clinical activities of the study patients. In all study patients, the imaging studies were performed within 3 months of ileocolonoscopy (median interval, 8 days; interquartile range [IQR], 3–18).

Definition of the patient groups

Deep healing (DH) was defined as the presence of both EH and RH, and nonhealing (NH) was defined as the absence of both EH and RH. Accordingly, the study patients were classified into 4 groups: DH, EH-only, RH-only, and NH groups.

Study endpoints

The primary endpoint was major outcomes defined by the development of any of the following: the need for anti-TNF dose intensification, switch to other biologics, CD-related bowel resection, or hospitalization. Anti-TNF dose intensification was defined as doubling of the dose (infliximab, 5–10 mg/kg) or shortening of the interval (adalimumab, 40 mg every 2 weeks to every week). Switch to other biologics was defined as the switch to other anti-TNF agents, vedolizumab or ustekinumab. CD-related bowel resection was defined as the resection of any bowel segment

because of CD. The reasons for hospitalization included both CD activity and therapy-related complications or adverse events.

Statistical analysis

Categorical variables were expressed as numbers and percentages, and continuous variables were expressed as median and IQR. For comparisons among the 4 groups, the χ^2 test was used for categorical variables and the Kruskal-Wallis test was used for continuous variables. Kaplan-Meier survival analysis with the log-rank test was used to compare survival without major outcomes and each outcome among the 4 groups. If more than 1 major outcome occurred, survival analysis was performed based on the time of the first major outcome. Cox regression analysis was performed to identify factors associated with major outcomes. Variables with P values of <0.1 in the univariate Cox regression analysis were included in the multivariable Cox regression analysis. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 21.0 (IBM, Armonk, NY).

Ethical considerations

The study protocol was approved by the Institutional Review Board of Asan Medical Center (IRB no. 2020-0820).

RESULTS

Baseline characteristics and patient group classification

Among 516 patients with CD who received anti-TNF therapy at our center, 392 patients with CD who had received anti-TNF therapy for more than 1 year before endoscopic and radiologic evaluation (within 3-month intervals) and then followed for more than 1 year were included in this study. Of them, 261 patients (66.6%) were male, and the median disease duration was 9.5 years (IQR, 6–14). The median duration of anti-TNF treatment was 42.0 months (IQR, 19.0–67.8). According to the study definition, 114 (29.1%), 59 (15.1%), 41 (10.4%), and 178 patients (45.4%) were classified into the DH, EH-only, RH-only, and NH groups, respectively (Table 1).

Major outcomes in the study groups

The median follow-up duration was 18.0 months (IQR, 15.0–21.0), and there was no significant difference in the median follow-up duration among the study groups ($P = 0.39$) (Table 2). Overall, major outcomes occurred in a total of 123 patients (31.4%): 8 (7.0%) in the DH group, 14 (23.7%) in the EH-only group, 11 (26.8%) in the RH-only group, and 90 (50.6%) in the NH group (Table 2). Compared with the NH group, the incidence rates of major outcomes were significantly lower in the DH group ($P < 0.001$), EH-only group ($P < 0.001$), and RH-only group ($P = 0.006$). Moreover, the DH group showed a lower incidence of major outcomes than the EH-only group ($P = 0.002$) and the RH-only group ($P = 0.001$) as well. However, there was no significant difference between the EH-only group and the RH-only group ($P = 0.725$). Hospitalization occurred in 38 patients (9.7%): 3 (2.6%) in the DH group, 6 (10.2%) in the EH-only group, 4 (9.8%) in the RH-only group, and 25 (14.0%) in the NH group (Table 2).

Prognosis according to endoscopic healing and radiologic healing

In the Kaplan-Meier analysis, the rates of major outcome-free survival at 6, 12, 18, and 24 months were 80.6%, 74.5%, 68.7%, and 65.6% in the patients as a whole, 97.4%, 95.6%, 91.7%, and 91.7% in the DH group, 89.8%, 86.4%, 78.1%, and 70.4% in the EH-only group, 90.2%, 80.5%, 74.5%, and 66.2% in the RH-only group, and 64.6%, 55.6%, 49.7%, and 47.2% in the NH group, respectively. There were significant differences in the major outcome-free survival among the 4 groups ($P < 0.001$) (Figure 1). Specifically, the rate of major outcome-free survival was significantly higher in the DH group than in the EH-only group ($P = 0.001$), RH-only group ($P = 0.001$), and NH group ($P < 0.001$).

In the Kaplan-Meier survival analysis of anti-TNF dose intensification and switch to other biologics, there were significant differences in each outcome-free survival among the 4 groups (both $P < 0.001$). However, CD-related surgery-free survival had no significant differences among the 4 groups ($P = 0.114$). In case of hospitalization, the rates of hospitalization-free survival at 6, 12, 18, and 24 months were 95.9%, 93.1%, 90.4%, and 85.2% in the patients as a whole, 100.0%, 99.1%, 97.8%, and 83.8% in the DH group, 94.9%, 93.2%, 91.2%, and 88.0% in the EH-only group, 97.6%, 95.1%, 92.0%, and 73.6% in the RH-only group, and 93.3%, 88.8%, 85.2%, and 85.2% in the NH group, respectively. There were significant differences in the hospitalization-free survival among the 4 groups ($P = 0.016$), and the DH group showed a significantly higher hospitalization-free survival rate than did the EH-only group ($P = 0.041$) and the NH group ($P = 0.001$) (see Supplementary Figure S1, Supplementary Digital Content 1, http://links.lww.com/CTG/A738).

Factors associated with major outcomes

In the multivariable Cox regression analysis, elevated CRP (CRP $\geq$0.6 mg/dL) at baseline was significantly associated with the development of major outcomes (adjusted hazard ratio [aHR], 2.166; 95% confidence interval [CI], 1.508–3.110; $P < 0.001$) (Table 3). Moreover, NH was significantly associated with major outcomes (aHR, 8.844; 95% CI, 4.268–18.323; $P < 0.001$). EH-only and RH-only were also significantly associated with major outcomes, respectively (aHR, 3.903; 95% CI, 1.635–9.315; $P = 0.002$ in EH-only, aHR, 3.843; 95% CI, 1.545–9.558; $P = 0.004$ in RH-only). The results of Cox regression analysis for the factors associated with each outcome are provided in Supplementary Tables S1–S4 (see Supplemental Digital Content 2, http://links.lww.com/CTG/A739).

DISCUSSION

In this study, patients with CD who have achieved both EH and RH were less likely to develop major outcomes during the follow-up. We also observed that compared with combined EH and RH, EH-only was independently associated with the development of major outcomes.

Owing to poor correlations between clinical activity indices and more objective outcomes such as endoscopic findings and biomarkers including CRP, symptomatic/patient-reported outcome remission alone is no longer used as a therapeutic target of CD (5,7,9,31). Therefore, mucosal healing (MH) assessed by endoscopy has been used as a key outcome in several randomized controlled trials and identified as an important prognostic factor (32–35). By contrast, radiologic outcome has not been well established as the therapeutic target of CD. In the STRIDE consensus, MH on cross-sectional imaging was recommended as a therapeutic target when endoscopic evaluation is impossible (8). However, because of the nature of CD involving the whole layer of the bowel wall, MH defined by the absence of ulcerations in endoscopy or cross-sectional imaging may not be a sufficient target,

Table 1. Baseline characteristics of the patients according to the presence of endoscopic and radiologic healing

	Total (n = 392)	Deep healing (n = 114)	Endoscopic healing-only (n = 59)	Radiologic healing-only (n = 41)	Nonhealing (n = 178)	*P*
Male	261 (66.6)	76 (66.7)	37 (62.7)	30 (73.2)	118 (66.3)	0.75
Age at diagnosis						0.77
A1 (≤16)	72 (18.4)	24 (21.1)	8 (13.6)	9 (22.0)	31 (17.4)	
A2 (17–40)	303 (77.3)	87 (76.3)	47 (79.7)	30 (73.2)	139 (78.1)	
A3 (>40)	17 (4.3)	3 (2.6)	4 (6.8)	2 (4.9)	8 (4.5)	
Disease duration, yr	9.5 (6–14)	7 (4–12.3)	9 (7–13)	13 (7–16)	10 (6–14)	0.001
Interval from CD diagnosis to the commencement of anti-TNF therapy, mo	61.5 (21.0–110.8)	42.0 (8.0–96.0)	65.0 (25.0–127.0)	100.0 (56.5–147.5)	58.5 (28.8–114.0)	0.16
Interval from the commencement of anti-TNF therapy to index evaluation, mo	42.0 (19.0–67.8)	42.0 (15.8–68.3)	36.0 (13.0–67.0)	41.0 (18.5–64.0)	46.5 (24.0–75.35)	0.16
Smoking at diagnosis						0.72
Never	269 (68.6)	80 (70.2)	39 (66.1)	31 (75.6)	119 (66.9)	
Former	23 (5.9)	9 (7.9)	4 (6.8)	1 (2.4)	9 (5.1)	
Current	100 (25.5)	25 (21.9)	16 (27.1)	9 (22.0)	50 (28.1)	
Family history of IBD	35 (8.9)	10 (8.8)	3 (5.1)	3 (7.3)	19 (15.9)	0.60
Montreal location						0.077
Ileum (L1)	56 (14.3)	24 (21.1)	11 (18.6)	5 (12.2)	16 (9.0)	
Colon (L2)	18 (4.6)	7 (6.1)	1 (1.7)	2 (4.9)	8 (4.5)	
Ileocolon (L3)	318 (81.1)	83 (72.8)	47 (79.7)	34 (82.9)	154 (86.5)	
Montreal behavior						<0.001
Nonstricturing, nonpenetrating (B1)	128 (32.7)	55 (48.2)	17 (28.8)	5 (12.2)	51 (28.7)	
Stricturing (B2)	113 (28.8)	31 (27.2)	21 (35.6)	10 (24.4)	51 (28.7)	
Penetrating (B3)	151 (38.5)	28 (24.6)	21 (35.6)	26 (63.4)	76 (42.7)	
Perianal disease	240 (61.2)	68 (59.6)	29 (49.2)	23 (56.1)	120 (67.4)	0.070
History of intestinal resection	192 (49.0)	44 (38.6)	24 (40.7)	33 (80.5)	91 (51.1)	<0.001
Previous exposure to other anti-TNF agents	21 (5.4)	3 (2.6)	0 (0)	2 (4.9)	16 (9.0)	0.022
CRP, mg/dL	0.25 (0.1–0.8)	0.1 (0.1–0.6)	0.14 (0.1–0.5)	0.33(0.1–0.7)	0.52 (0.2–1.0)	<0.001
Elevated CRP (≥0.6 mg/dL)	129 (32.9)	27 (23.7)	12 (20.3)	13 (31.7)	77 (43.3)	0.001
Imaging modality						0.049
MRE	120 (30.6)	45 (39.5)	20 (33.9)	9 (22.0)	46 (25.8)	
CTE	272 (69.4)	69 (60.5)	39 (66.1)	32 (78.0)	132 (74.2)	

Continuous variables are expressed as median (interquartile range). Nominal and ordinal variables are expressed as numbers (percentages).
CD, Crohn's disease; CRP, C-reactive protein; CTE, computed tomography enterography; IBD, inflammatory bowel disease; MRE, magnetic resonance enterography; TNF, tumor necrosis factor.

and transmural healing (TH) could be a more desirable goal. Notably, the Lémann index was recently developed to evaluate the improvement of bowel wall damage after treatment (36).

As cross-sectional imaging modalities, CTE, MRE, and IUS have been evaluated as tools for assessing RH in patients with CD. Laterza et al. (17) assessed CTE in addition to clinical and endoscopic evaluation and concluded that radiological evaluation can provide complementary information for predicting prognosis, especially for the hospitalization rate in patients with CD with higher transmural activity. MRE is the most widely studied modality for evaluating RH in patients with CD, and several studies have reported that an MRE response of small bowel lesions among patients with CD was associated with a decreased risk of the following outcomes: adding other medications or increasing the dose of current medications (37), biochemical relapse (38), clinical relapse (37–39), surgery (38,39), surgical or endoscopic intervention

Table 2. Major outcomes and CD-related hospitalization during the follow-up according to endoscopic and radiologic healing

	Total (n = 392)	Deep healing (n = 114)	Endoscopic healing-only (n = 59)	Radiologic healing-only (n = 41)	Nonhealing (n = 178)	*P*
Duration of follow-up after index evaluation, mo, median (IQR)	18.0 (15.0–21.0)	18.0 (15.0–21.0)	19.0 (16.0–21.0)	20.0 (16.5–22.0)	18.0 (14.0–21.0)	0.39
Major outcomes, n (%)	123 (31.4)	8 (7.0)	14 (23.7)	11 (26.8)	90 (50.6)	<0.001
Anti-TNF dose intensification, n (%)	69 (17.6)	6 (5.3)	8 (13.6)	7 (17.1)	48 (27.0)	<0.001
Switch to other biologics, n (%)	44 (11.2)	0 (0)	3 (5.1)	1 (2.4)	40 (22.5)	<0.001
CD-related bowel resection, n (%)	13 (3.3)	1 (0.9)	3 (5.1)	0 (0)	9 (5.1)	0.12
Hospitalization, n (%)	38 (9.7)	3 (2.6)	6 (10.2)	4 (9.8)	25 (14.0)	0.016

CD, Crohn's disease; IQR, interquartile range; TNF, tumor necrosis factor.

(18), and hospitalization (37,38). In a recent multicenter prospective study, an early transmural response at week 12 after the commencement of anti-TNF agents for patients with CD could predict corticosteroid-free deep remission at week 52 (20). Moreover, the achievement of clinical remission (CDAI <150), biochemical remission (both CRP <0.5 mg/dL and fecal calprotectin <250 μg/g), and a score of the transmural response of ≥2 were shown to predict corticosteroid-free deep remission at week 52 with a positive predictive value of 100% (20). IUS can also be used to evaluate the cross-sectional bowel wall healing status without the need for radiation exposure. IUS findings, such as bowel wall thickness, color Doppler grade, parietal enhancement, and the presence of transmural complications or stenosis, have been reported to be associated with surgery (40), change or intensification in medication or surgery (41), and an overall poor outcome (42).

The value of combined EH and RH was also evaluated in recent studies. Fernandes et al. (16) analyzed 214 patients with CD who underwent an MRE and a colonoscopy within a 6-month interval and found that the group who achieved both normal MRE and normal endoscopy had lower rates of therapy escalation, surgery, and hospitalization during 1 year of the follow-up compared with the EH-only group and those with an active endoscopy, irrespective of MRE findings. Castiglione et al. (19) used ileocolonoscopy and IUS to evaluate TH in 218 patients with CD who received anti-TNF therapy for 2 years; in that study, patients with both TH (bowel wall thickness ≤3 mm in IUS) and MH (defined by Simple Endoscopic Score for Crohn's Disease ≤2) showed a higher rate of corticosteroid-free clinical remission, lower rates of hospitalization, and surgery at 1 year compared with the MH-only group and a group with both endoscopic activity and sonographic wall thickness >3 mm. Lafeuille et al. (21) found that combined EH and MRE healing was independently associated with a decreased risk of bowel damage progression, major outcomes (surgery, progression of bowel damage, or hospitalization), and relapse-related drug discontinuation compared with EH-only.

Previous studies classified patients with CD into 3 groups according to endoscopic and radiologic findings and compared their prognosis (16,19). In this study, we classified patients into 4 groups according to the presence of EH and RH and only 1 previous study classified patients into 4 groups similar to ours (21). Compared with NH, DH was associated with a better prognosis for major outcomes, which is in line with the findings of previous studies (19,21). We were also able to show the independent association between major outcomes and EH-only compared with DH. Another notable finding is the superior major outcome-free survival rate of the DH group compared with the RH-only group ($P = 0.001$). This is in contrast to the results of a previous study that suggested a similar prognosis between patients with endoscopic inflammation, but without MRE activity and those with both normal MRE and normal endoscopy (16). Overall, our study findings reinforce the concept that the therapeutic target for patients with CD needs to be upgraded to a higher level, which is to achieve both EH and RH.

The strength of our study is that among the studies on this topic, our study has the longest follow-up duration and the largest number of patients. Endoscopic and radiologic tests were performed within 3-month intervals, and both tests were reevaluated by board-certified specialists who were blinded to the results of other tests to reduce bias. For evaluating prognosis, more objective outcomes were used rather than clinical activity indices. In

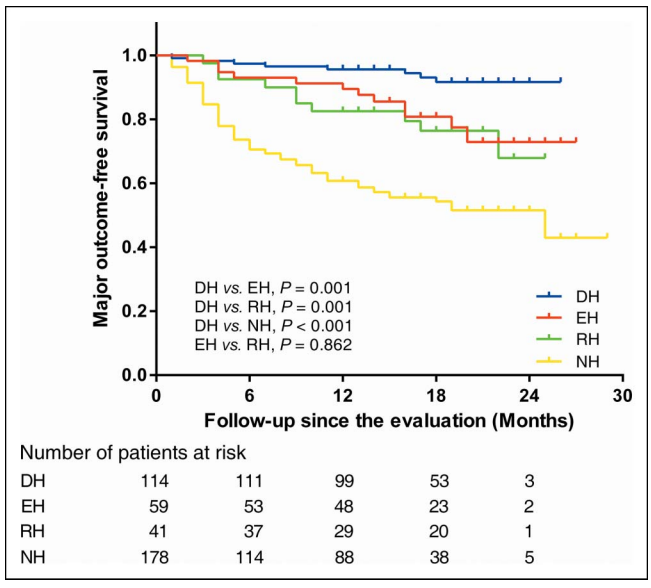

Figure 1. Kaplan-Meier curves for major outcome-free survival according to EH and RH. Differences in the cumulative survival rates without major outcomes were compared by the log-rank test. DH, deep healing; EH, endoscopic healing-only; NH, nonhealing; RH, radiologic healing-only.

Table 3. Univariate and multivariable Cox regression analysis for factors associated with major outcomes

	Univariate analysis			Multivariable analysis		
	HR	95% CI	*P*	aHR	95% CI	*P*
Male	0.876	0.606–1.267	0.48			
Age at diagnosis						
A1 (≤16)	Reference	Reference	Reference			
A2 (17–40)	0.705	0.461–1.078	0.11			
A3 (>40)	0.679	0.262–1.759	0.43			
Disease duration, yr	0.993	0.962–1.026	0.69			
Interval from CD diagnosis to the commencement of anti-TNF therapy, mo	1.000	0.997–1.003	0.92			
Duration of anti-TNF therapy, mo	0.998	0.993–1.004	0.56			
Smoking						
Never	Reference	Reference	Reference			
Former	1.135	0.550–2.343	0.73			
Current	0.876	0.575–1.335	0.54			
Montreal location						
Ileum (L1)	Reference	Reference	Reference			
Colon (L2)	0.845	0.278–2.567	0.77			
Ileocolon (L3)	1.424	0.815–2.487	0.22			
Montreal behavior						
Nonstricturing, nonpenetrating (B1)	Reference	Reference	Reference			
Stricturing (B2)	1.190	0.740–1.916	0.47			
Penetrating (B3)	1.507	0.979–2.321	0.063			
Perianal disease	1.253	0.863–1.820	0.24			
History of intestinal resection	1.225	0.859–1.747	0.26			
Previous exposure to other anti-TNF agents	1.745	0.913–3.335	0.092	1.033	0.536–1.991	0.92
Elevated CRP (≥0.6 mg/dL)	2.681	1.881–3.822	< 0.001	2.166	1.508–3.110	<0.001
Healing status						
Deep healing	Reference	Reference	Reference	Reference	Reference	Reference
Endoscopic healing-only	3.630	1.523–8.655	0.004	3.903	1.635–9.315	0.002
Radiologic healing-only	4.039	1.624–10.042	0.003	3.843	1.545–9.558	0.004
Nonhealing	9.979	4.836–20.593	< 0.001	8.844	4.268–18.323	<0.001

aHR, adjusted hazard ratio; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; TNF, tumor necrosis factor.

addition, the number of patients included in our study was larger than that of previous studies (16,19,21). The statistical power calculated based on a previous study (21) was >0.999 with 114 patients in the DH group and 59 patients in the EH-only group, which implies sufficient power.

However, this study entails certain limitations. First, its retrospective design has a possibility of information bias. However, the main data used in our study had been prospectively collected and recorded. Second, the single-center-based study design may limit the generalizability of our study results. However, in South Korea, most of the patients with moderate-to-severe CD requiring anti-TNF therapy are treated at tertiary centers and not referred back to primary or secondary institutions even after the commencement of anti-TNF therapy (24). Therefore, our patient population may sufficiently represent Korean patients with CD receiving anti-TNF therapy. Third, 2 types of radiologic studies (CTE and MRE) were used in our study. However, another previous study also included patients with CD evaluated by CTE or MRE and analyzed those patients together (43) in a manner similar to our previous study (24). Fourth, there were differences in the interval from CD diagnosis to the first anti-TNF commencement and Montreal behavior at baseline, which might have affected the prognosis of patients with CD. However, those factors were not statistically significant in the Cox regression analyses. Fifth, individual major outcomes could not be properly compared between groups because the number of each event was small. Finally, we used a dichotomous definition of healing/NH rather than a scoring system for endoscopic and radiologic evaluation.

However, because our study used real-life practice data, a simple definition of activity/inactivity would be more practical to use than complex endoscopic scoring systems, such as the Crohn's Disease Endoscopic Index of Severity and the Simple Endoscopic Score for Crohn's Disease. For radiologic evaluation, a simple definition is more feasible because no validated scoring system is available for CTE, and the MRE scoring system is not recommended in clinical practice (44). Moreover, there is a critical need for establishing a consensus on the definition of RH (45). Whether achieving combined EH and RH can significantly improve the disease course of patients with CD should also be elucidated in a targeted study.

Patients with CD under anti-TNF therapy who achieved both EH and RH had a significantly lower risk of major outcomes compared with patients who only achieved EH. Our observation suggests that therapeutic targets of CD need to be set to a higher level as achieving both EH and RH. Further prospective trials with both MH and RH as therapeutic targets are needed to define the most appropriate treatment goal of CD.

CONFLICTS OF INTEREST

Guarantor of the article: Byong Duk Ye, MD, PhD.

Specific author contributions: Conception and design of the study: K.H.O., E.H.O., and B.D.Y. Acquisition of data: K.H.O., E.H.O., S.M.N., Seong H.P., S.W.H., Sang H.P., D.-H.Y., J.-S.B., S.-J.M., S.-K.Y., and B.D.Y. Analysis and interpretation of data: K.H.O. and B.D.Y. Drafting of the manuscript: K.H.O. and B.D.Y. Critical revision of the manuscript for important intellectual content and study supervision: B.D.Y. All authors approved the final version of the manuscript.

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Study Highlights

WHAT IS KNOWN

✓ Endoscopic healing is currently recommended as the therapeutic target in patients with Crohn's disease.

WHAT IS NEW HERE

✓ Achieving both endoscopic and radiologic healing shows a better prognosis than endoscopic healing only in patients with Crohn's disease.

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