Early Biological Therapy Within 12 Months of Diagnosis Leads to Higher Transmural Healing Rates in Crohn's Disease

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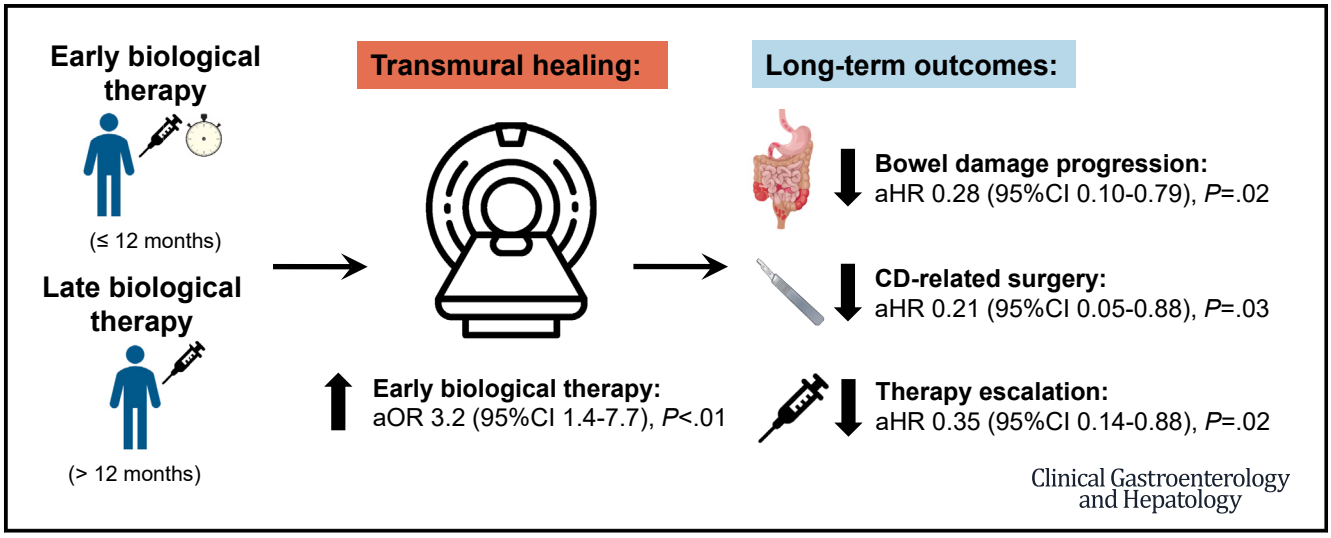

BACKGROUND & AIMS: **Transmural healing (TH) is emerging as a potential Crohn's disease (CD) treatment target. Early biological treatment seems to be associated with improved disease outcomes, but its impact on TH remains unclear. We aimed to assess the impact of early biological treatment initiation on TH and its influence on CD prognosis.**

METHODS: **This multicenter retrospective study included adult patients with CD starting biological therapy. TH was assessed using magnetic resonance enterography (MRE) at 12 ± 6 months post-therapy initiation, with radiological examinations reviewed by blinded expert radiologists.**

Abbreviations used in this paper: aHR, adjusted hazard ratio; Anti-TNF, TNF-alpha inhibitors; aOR, adjusted odds ratio; BWT, bowel wall thickness; CD, Crohn's disease; CI, confidence interval; CTE, computed tomography enterography; EH, endoscopic healing; HR, hazard ratio; IBD, inflammatory bowel disease; IFX, infliximab; IQR, interquartile range; MRE, magnetic resonance enterography; OR, odds ratio; PRO2, Patient-Reported Outcomes 2; SES-CD, Simple Endoscopic Score for CD; TH, transmural healing; TNF, tumor necrosis factor.

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TH was defined as complete normalization of all MRE parameters. Timing of biological therapy initiation was analyzed as a continuous variable, with optimal cutoff determined using the Youden index and clinical relevance. Logistic regression with propensity score-adjusted analysis was used to assess the association between early biological therapy initiation and TH. Long-term outcomes (bowel damage progression, CD-related surgery, CD-flare hospitalization, and therapy escalation) were evaluated.

RESULTS: **Among 154 patients with CD, early biological therapy initiation within 12 months of diagnosis was associated with significantly higher TH rates (adjusted odds ratio [aOR], 3.23; 95% confidence interval [CI], 1.36–7.70; $P < .01$), which persisted after adjusting for previous biological therapy use (aOR, 2.82; 95% CI, 1.13–7.06; $P = .03$). Time-to-event analysis demonstrated that TH was significantly associated with reduced risk of bowel damage progression (adjusted hazard ratio [aHR], 0.28; 95% CI, 0.10–0.79; $P = .02$), CD-related surgery (aHR, 0.21; 95% CI, 0.05–0.88; $P = .03$) and therapy escalation (aHR, 0.35; 95% CI, 0.14–0.88; $P = .02$), independently of early biological therapy.**

CONCLUSIONS: **Early initiation of biological therapy within 12 months of diagnosis significantly increases TH rates, leading to improved long-term outcomes in patients with CD.**

Keywords: Biologic; Crohn's Disease; Early; Magnetic Resonance Enterography; Transmural Healing.

Crohn's disease (CD) is a progressive disease with approximately one-half of the patients developing a complicated phenotype (stricturing or penetrating) within 10 years of the disease.[1] Although endoscopic healing (EH) has been considered the best treatment target, CD is a transmural disease, and transmural healing (TH) or radiological healing, assessed by cross-sectional imaging, has recently been shown to associate with improved outcomes as compared with EH alone, such as higher rates of steroid-free clinical remission and lower rates of hospitalization and need for surgery.[2-5] Moreover, early transmural response seems to be a predictor of corticosteroid-free remission at 1 year of anti-tumor necrosis factor (TNF) therapy.[6] Therefore, although TH is not yet considered a formal treatment target in CD, it was proposed as a potential target of interest in the STRIDE II consensus.[7]

Aligned with the tight monitoring and treat-to-target strategies, the concept of early intervention has emerged in CD. Several studies have shown that there may be a window of opportunity where therapies may be more effective and that the early use of biologics leads to higher rates of clinical remission, lower relapse rates, and higher EH rates when compared with late biologic initiation.[8-12]

However, to our knowledge, there is no information about the impact of the timing of biological therapy initiation on the chances of achieving TH, and how it translates into improved outcomes for patients with CD. This study aimed to assess the impact of early biologic initiation on TH rates and their impact on the long-term follow-up of patients with CD.

Methods

Study Design and Population

This was a multicenter European retrospective study including adult patients with CD who were started on any biological therapy for induction of remission of intestinal luminal disease. To be included, patients needed baseline cross-sectional imaging (computed tomography enterography [CTE] or magnetic resonance enterography [MRE]) to confirm the presence of transmural inflammation before treatment initiation. Additionally, they required at least 1 follow-up MRE at 12 ± 6 months post-biological initiation. Patients with previous biological therapy or with a prior history of surgery before treatment initiation could be included as long there was evidence of transmural inflammation. Patients who started biological therapy for postoperative recurrence prophylaxis, perianal disease, and/or extraintestinal manifestations without signs of active luminal inflammation were excluded.

Transmural Healing Assessment

Radiological evaluation was locally conducted by at least 1 experienced (>10 years of experience) inflammatory bowel disease (IBD) radiologist from each center. Before imaging review, an investigator's meeting took place to define the lesions detected by CTE and MRE and to standardize the assessment across centers (Table 1). Every cross-sectional imaging was reviewed, and data was collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Sociedade Portuguesa de Gastrenterologia (Portuguese Society of Gastroenterology) – CEREGA.[13,14] Radiologists were blinded to clinical and endoscopic information but not to baseline CTE/MRE. Clinical data were collected by a gastroenterologist blinded to the radiological evaluation. Each examination was reviewed for assessment for active intestinal inflammation (increased bowel wall thickness [BWT], presence of ulceration, edema, or increased contrast enhancement), peri-enteric inflammation (fat stranding, free fluid, or engorgement of the

vasa recta), and CD-related complications (stricture, sinus tract/fistula, abscess, or inflammatory mass) for each intestinal segment (jejunum, proximal ileum, terminal ileum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum), according to ECCO-ESGAR definitions (Table 1).[15] Given the intra-segment heterogeneity, mural abnormalities were measured in the most affected section (ie, the most thickened). TH was defined by consensus as a complete normalization of all MRE parameters, including absence of intestinal inflammation, absence of peri-enteric inflammation, and no CD-related complications.[4]

Early Biological Treatment Definition

As per the "Paris definition," early CD is characterized by a disease duration of $\leq$18 months, with no prior or current treatment involving immunomodulators or biologics.[16] However, across studies, there lacks a clear consensus on the definition of early biological treatment, ranging from 12 to 24 months. In this study, we defined the timing of biological therapy initiation as a continuous variable from the date of diagnosis (date of the diagnostic endoscopy or surgery). This approach allowed us to calculate the optimal cutoff for defining the ideal timing for early biological treatment initiation to achieve TH, which in turn, facilitated the categorization of early vs late biological treatment initiation.

Outcomes

The primary outcome of this study was the achievement of TH assessed by MRE at 12 $\pm$ 6 months following biological therapy initiation. The secondary outcomes were assessed at 2 different time points, including at 12 $\pm$ 6 months following biological initiation (T1) and the end of the follow-up (T2). At T1, we assessed as exploratory secondary endpoints the presence of MRE response (defined as absence of ulceration, edema, increased contrast enhancement, peri-enteric inflammation, and CD-related complications despite the persistence of increased BWT) and the individual healing of severe MRE lesions. We also assessed the presence of EH defined as a Simple Endoscopic Score for CD (SES-CD) $<$3 or absence of ulcers, and clinical remission defined according to patient-reported outcome 2 ([PRO2]-abdominal pain score $\leq$1 and stool frequency $\leq$3) and/or according to the physician's global assessment. At T2, as secondary long-term outcomes, we assessed bowel damage progression (defined as need for intestinal resection, presence of new stricture or fistula, or worsening of pre-existing stricture [increase in equivocal prestenotic dilation on imaging or occurrence of major obstructive symptoms] or fistula [new abscess or new fistula tract]),[4] CD-related surgery (intestinal resection excluding perianal surgery), hospitalization due to a CD-flare, and therapy escalation (defined as the need to switch biologic due to therapeutic failure and/or immunogenicity).

What You Need to Know

Background

Transmural healing (TH) has been proposed as a treatment target for Crohn's disease, yet the reported rates in the literature are low. The impact of early biological treatment on TH remains uncertain.

Findings

Early initiation of biological treatment within 12 months of diagnosis is associated with significantly higher TH rates. Achieving TH after 1 year of biological therapy is independently associated with improved outcomes.

Implications for patient care

When warranted, biological therapy should be started early (within 12 months from diagnosis) for patients with Crohn's disease, with TH deemed as a treatment target because it is associated with improved disease outcomes.

Statistical Analysis

A descriptive analysis was conducted to assess baseline characteristics. Continuous variables were summarized using mean and standard deviation for normally distributed data, and median and interquartile range (IQR) for non-normally distributed data. Categorical variables were presented as frequencies and proportions. The Student *t*-test was used for normally distributed continuous variables and the Wilcoxon rank-sum test for non-normally distributed ones. The χ^2 test was used to compare categorical variables.

The Youden Index and clinical relevance were used to calculate the best cutoff for early biological treatment initiation. The association between the timing of initiation of the biological therapy and the presence of TH and MRE response was analyzed using univariate and propensity score-adjusted logistic regression. To estimate the propensity score, a logistic regression model using early biological therapy as the dependent variable was performed. The covariates included were age at diagnosis, ileal involvement (L1 and L3), perianal disease, active smoking, large or deep ulcers at baseline endoscopy, disease extent at baseline cross-sectional imaging, BWT of the most affected segment at baseline, radiological stricture, and penetrating disease. Previous biological exposure was not included in the model as almost all patients previously exposed to biologics were in the late biological treatment group. Therefore, we adjusted for this variable in subsequent analyses. The propensity score was then included as a linear term in an adjusted logistic regression model. The individual healing of MRE

Table 1. Definition of Radiological Lesions

Luminal and extra-luminal signs of active disease		
Lesion	Definition	Specification
BWT	Abnormal BWT is defined when >3 mm on the most thickened section	Measurement perpendicular to the bowel lumen.
Ulcers	Small focal breaks in the inner surface of a thickened bowel wall with focal extension of air or enteric contrast into the inflamed wall	Ulcers are not present without edema (mimicker: post-inflammatory pseudo-polyps). Do not extend beyond the bowel wall (otherwise rate as sinus tract). To increase reader confidence in diagnosing ulcers on MRE, the detection of this finding on 2 different planes or sequences is recommended
Edema	Increased signal intensity on T2 sequences compared with the signal on normal appearing bowel loops or to the psoas muscle.	Ideally assessed in T2-weighted images with fat saturation. Persistence of high signal intensity after fat saturation confirms the presence of edema and rules out the possibility of fatty infiltration. Not assessable by CT scan.
Increased contrast enhancement	Bowel wall signal greater than normal appearing bowel loops.	Rate as "present" regardless of the pattern of enhancement (homogeneous, inner-wall or halo sign).
Engorgement of the vasa recta	Engorgement of peri-enteric vasculature (regional dilation of the vasa recta).	
Perienteric fat stranding	Increase in mesenteric signal seen on gadolinium-enhanced and/or T2-weighted sequences causing loss of the typical sharp interface between intestinal wall and mesentery.	
Perienteric free fluid	Free fluid surrounding abnormal bowel segments.	May range from small rim to moderate amount of fluid.
Stricture	Luminal narrowing accompanied by unequivocal dilatation (upstream bowel segment $\geq$ 3 cm). When upstream lumen is not equivocally dilated (2 - 3 cm), but multiple pulse sequences or fluoroscopic observation demonstrated fixed narrowing without upstream dilation, it is appropriate to describe that a probable stricture is present.	Most accepted definition of stricture.
Fistula	Tubular structures arising from the bowel wall with fluid and/or air content exhibiting peripheral contrast enhancement connecting the bowel lumen with other anatomical structures (the most frequent are other bowel segments, the skin, or the bladder).	After healing, fistulas may have low signal on T2-weighted images with minimal enhancement. Residual post-treatment fistulas were not considered as "fistula present."
Sinus tract	Tubular structures arising from the bowel wall with fluid and/or air content exhibiting peripheral contrast enhancement connecting the bowel lumen with the mesentery.	
Abscess	Mesenteric or peritoneal fluid collection with rim enhancement walls.	May contain gas.
Inflammatory mass	Ill-defined mass-like process of mixed fat and/or soft tissue signal intensity (not containing fluid signal intensity).	Usually associated with penetrating disease, such as complex fistulas.

BWT, bowel wall thickness; CT, computed tomography; MRE, magnetic resonance enterography.

lesions after 1 year of biological therapy was analyzed using the McNemar test. To assess the impact of early biological therapy and TH on long-term outcomes, a survival analysis incorporating Cox regression analysis was performed. Cox regression analysis was also performed to assess the impact of MRE response and the

persistence of individual MRE lesions on long-term outcomes. Statistical analysis was conducted with Stata package version 16.

Sample Size Calculation

According to the study performed by Castiglione et al, anti-TNF therapy can lead to TH in approximately 30% of the patients at 1 year of therapy.[5] Moreover, early biological use seems to lead to higher EH rates, with an odds ratio (OR) of 2.37.[12] Therefore, assuming a probability of TH in patients under biological therapy of 30% and considering an OR of 2.5 for higher TH rates in patients with an early biological therapy introduction, a total of 160 patients were deemed necessary to ensure 80% power, with a significance level (alpha) of 0.05.

Results

Population Characteristics

We included 154 patients diagnosed with CD from 1975 to 2022. There was a similar gender distribution (51% female patients), and the median age at diagnosis was 26 years (IQR, 20–36 years). The median time between the first cross-sectional imaging and treatment initiation was 1 month (IQR, 0–2.5 months). Predominantly, patients exhibited involvement of the ileal or ileocolonic region (95%), with 47% demonstrating the presence of inflammatory, 31% stricturing, and 22% penetrating behavior. Before initiating biological therapy, 23% of the patients had undergone CD-related surgery.

Regarding the time of initiation of the biological therapy, 38% (n = 59) started a biological within 12 months, and 47% (n = 73) started within 24 months of diagnosis.

Approximately one-fifth of patients (21%; n = 32) achieved TH at 12 ± 6 months following biological initiation. Moreover, 73% (n = 112) were in clinical remission, and among the 82 patients who underwent endoscopic evaluation, 48% (n = 39) achieved EH.

Baseline characteristics according to the achievement of TH are summarized in Table 2. Patients who achieved TH tended to have a milder radiological disease with shorter disease extent on cross-sectional evaluation, lower BWT, and lower rates of stricture or penetrating disease, including fistula, sinus tract, abscess, or inflammatory masses (Table 2). Thirty-two patients (21%) had already been exposed to a previous biological therapy. Although the proportion of patients previously exposed to biological therapy was numerically higher in the group not achieving TH, this difference did not reach statistical significance.

Early Biological Therapy and Transmural Healing Rates

The median duration of disease until the initiation of biological therapy among patients who achieved TH was significantly shorter compared with those who did not achieve TH (10 [IQR, 3–74] vs 59 [IQR, 9–197] months; $P = .01$) (Table 2). Using univariate logistic regression analysis and considering the timing of biological therapy initiation as a continuous variable, early biological therapy was found to be associated with a higher TH rate (OR, 0.99; 95% confidence interval [CI], 0.991–0.999; $P = .04$). We determined a cutoff of 12 months as the optimal timing for early biological therapy initiation to achieve TH. The baseline differences between the early and late biological treatment groups are available in Supplementary Table 1.

When applying the 12-month cutoff, patients who started early biological therapy had 3 times greater odds of achieving TH when compared with patients who started late biological therapy (OR, 3.0; 95% CI, 1.35–6.67; $P < .01$). Using a multivariate regression analysis with a propensity score-adjusted model, early biological therapy initiation was associated with significantly higher TH rates (adjusted odds ratio [aOR], 3.23; 95% CI 1.36–7.70; $P < .01$). Adjusting this model for previous biological use, early biological therapy initiation was still associated with higher TH rates (aOR, 2.82; 95% CI, 1.13–7.06; $P = .03$) (Figure 1). Moreover, a sensitivity analysis focused exclusively on the 128 patients diagnosed after 1998 (when the first biological therapy became available) yielded similar results to the main analysis (aOR, 2.90; 95% CI, 1.16–7.21; $P = .02$).

Of the 41 patients with baseline cross-sectional involvement of the colon, 49% (n = 20) achieved TH. In contrast, only 20% (n = 28) of the 137 patients with small bowel involvement achieved TH. Regarding the impact of early biological treatment on TH rates according to disease location, propensity score-adjusted logistic regression showed that early biological therapy was not associated with higher colonic TH rates (aOR, 1.6; 95% CI, 0.4–6.8; $P = .5$), whereas there was a tendency for higher small bowel TH rates (aOR, 2.4; 95% CI, 0.98–5.8; $P = .057$).

MRE Response and Individual Healing of MRE Lesions

Among patients who did not achieve TH, 9 (7%) exhibited an MRE response. Thus, within the entire study population, 27% (n = 41) were deemed to have experienced an MRE response. Similar to TH rates, a statistically significant difference in MRE response rates was observed between patients who started early compared with late biological therapy, although this difference was less pronounced when compared with TH rates (TH rates, 32% vs 14%; $P < .01$; MRE response rates, 36% vs 22%; $P = .047$) (Figure 2).

Regarding the individual healing of MRE lesions, all lesions demonstrated a significant change from baseline evaluation, except for radiological strictures, which exhibited a non-significant reduction, for both the early and late biological treatment groups. The most prevalent persistent lesions in both groups included BWT, increased contrast enhancement, and strictures. Notably,

Table 2. Baseline Characteristics According to the Achievement of TH

	TH (21%; n = 32)	No TH (79%; n = 122)	*P*-value
Age at diagnosis, *years*	25 (19–30)	26 (20–38)	.4
Male gender	41 (13)	51 (62)	.3
Disease duration until biological initiation, *months*	10 (3–74)	59 (9–197)	**< .01**
Disease location			.5
Ileal (L1)	47 (15)	53 (64)	
Colonic (L2)	9 (3)	4 (5)	
Ileo-colonic (L3)	44 (14)	43 (53)	
Upper GI involvement (L4)	9 (3)	10 (12)	.9
Disease behavior			.1
Inflammatory (B1)	62 (20)	43 (53)	
Stricturing (B2)	19 (6)	34 (41)	
Fistulizing (B3)	19 (6)	23 (28)	
Perianal disease	34 (11)	29 (35)	.5
Smoking	31 (10)	37 (45)	.5
Endoscopic evaluation (maximum 3 months before biologic)			
Deep ulcers	33 (7)	38 (29)	.7
Large ulcers	38 (8)	18 (14)	**.049**
Strictures	29 (6)	49 (39)	.09
Cross-sectional imaging at baseline			
Extension of disease, *mm*	50 (11–150)	100 (45–190)	**.03**
BWT most affected segment, *mm*	6.8 (5–8)	8 (6.5–9.2)	**< .01**
Increased contrast enhancement	91 (29)	93 (114)	.6
Engorgement of the vasa recta	62 (20)	70 (86)	.4
Perienteric fat stranding	41 (13)	58 (71)	.1
Perienteric free fluid	9 (3)	12 (15)	.6
Stricture	12 (4)	46 (56)	**< .01**
Penetrating disease	12 (4)	32 (39)	**.03**
Biologic started			.4
Infliximab	62 (20)	53 (65)	
Adalimumab	25 (8)	38 (47)	
Vedolizumab	0 (0)	1 (1)	
Ustekinumab	12 (4)	7 (9)	
Biologic-naïve	88 (28)	77 (94)	.2
Concomitant thiopurines	69 (22)	62 (76)	.5

Note: Data are presented as percentage (number) or median (interquartile range).
Note: Bold *P* values indicate statistical significance.
BWT, Bowel wall thickness; GI, gastrointestinal; TH, transmural healing.

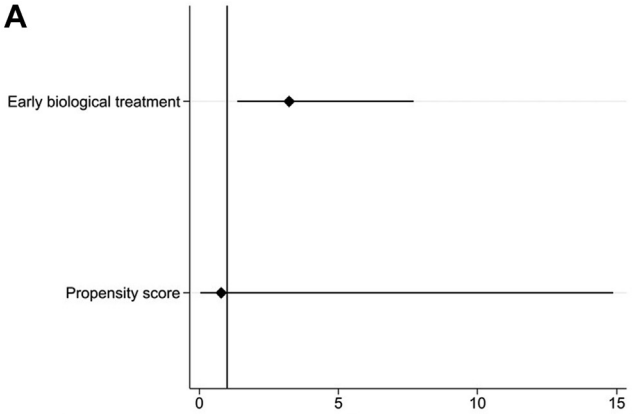
the persistence of these lesions appeared to be higher in the group undergoing late biological treatment (Table 3).

Long-term Outcomes

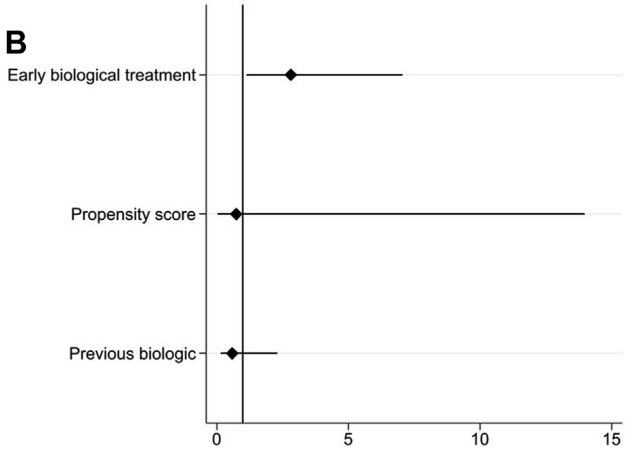
Patients were followed up for a median of 68 months (IQR, 39–94 months) following biological therapy initiation. Fifty-seven patients (37%) had bowel damage progression, 26% (n = 40) needed a CD-related surgery, 23% (n = 35) had a CD-related hospitalization, and 35% (n = 54) required therapy escalation.

Achieving TH within 1 year following therapy initiation was associated with a significantly reduced risk of bowel damage progression (12.5% vs 43.4%; $P = .001$), CD-related intestinal surgery (6.2% vs 31.2%; $P = .004$), and need for therapy escalation (15.6% vs 40.2%; $P = .01$), with a trend towards a decreased risk of CD-related hospitalization (9.7% vs 26.2%; $P = .05$).

In time-to-event analysis, patients achieving TH after 1 year of biological therapy exhibited a significantly longer time until bowel damage progression (hazard ratio [HR], 0.25; 95% CI, 0.09–0.70; $P = .008$), CD-intestinal surgery (HR, 0.20; 95% CI, 0.05–0.81; $P = .025$), and therapy escalation (HR, 0.35; 95% CI, 0.14–0.89; $P = .03$). No differences were observed until CD-related hospitalization (Figure 3). Conversely, early initiation of biological therapy was solely associated with a longer time until bowel damage progression (HR, 0.47;



Variables	OR (95% CI)	*p-value*
Early biological treatment (≤12 months from diagnosis)	3.23 (1.36-7.70)	**<0.01**
Propensity score	0.78 (0.04-14.86)	0.87



Variables	OR (95% CI)	*p-value*
Early biological treatment (≤12 months from diagnosis)	2.82 (1.13-7.06)	**0.03**
Propensity score	0.74 (0.04-13.98)	0.84
Previous biological treatment	0.59 (0.15-2.30)	0.45

Figure 1. Logistic regression with a propensity score-matched analysis on the impact of early biological treatment in TH rates. (*A*) Multivariate analysis using propensity score; (*B*) multivariate analysis using propensity score and adjusted for previous biological use.

95% CI, 0.26–0.86; $P = .015$). In a multivariable analysis, adjusted for early biological therapy, achieving TH remained significantly associated with a reduced risk of bowel damage progression (adusted hazard ratio [aHR], 0.28; 95% CI, 0.10–0.79; $P = .02$), CD-related intestinal surgery (aHR, 0.21; 95% CI, 0.05–0.88; $P = .03$), and therapy escalation (aHR, 0.35; 95% CI, 0.14–0.88; $P = .02$).

Achieving MRE response was also associated with longer time to bowel damage progression (HR, 0.30; 95% CI, 0.13–0.67; $P < .01$), CD-related surgery (HR, 0.20; 95% CI, 0.06–0.65; $P < .01$), CD-flare hospitalization (HR, 0.33; 95% CI, 0.12–0.93; $P = .04$), and therapy escalation (HR, 0.39; 95% CI, 0.18–0.82; $P = .01$). Increased contrast enhancement, one of the most prevalent persistent lesions on MRE, was the only variable significantly associated with an increased risk of all the long-term outcomes (Supplementary Table 2).

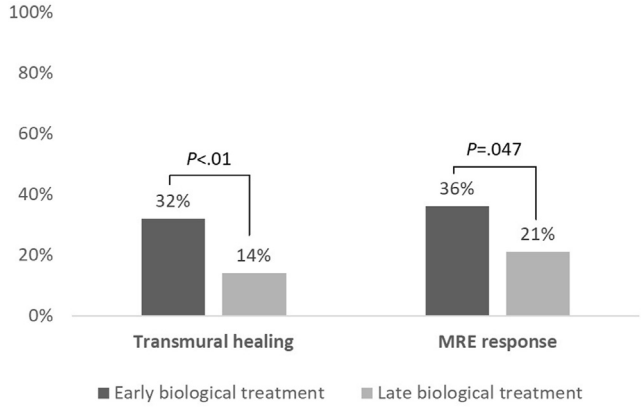


Figure 2. TH and MRE response rates according to the time of initiation of biological treatment (early: ≤12 months from diagnosis; late: >12 months from diagnosis).

Discussion

Herein, we have shown that starting biological treatment within the first year of CD diagnosis is associated with significantly higher TH rates and that achieving TH after 1 year of biological therapy is independently associated with improved long-term outcomes.

The management of CD has shifted focus towards achieving disease remission, with treatment targets evolving from clinical to biochemical and endoscopic remission. However, CD is a transmural disease and despite achieving EH, 75% of patients still present with luminal strictures on MRE and 32% with increased BWT.[17] Because this persistent wall damage may be associated with ongoing inflammation, recent studies have advocated TH as a possible new target for CD.[4] Furthermore, TH has been shown to improve long-term outcomes during a 5-year follow-up period.[18] In our study, using a definition of TH based solely on radiological evaluation and, adjusting for early biological therapy initiation, we demonstrated that TH is independently associated with reduced risk of bowel damage progression (aHR, 0.28; 95% CI, 0.10–0.79; $P = .015$), need for CD-intestinal surgery (aHR, 0.21; 95% CI, 0.05–0.88; $P = .03$), and therapy escalation (aHR, 0.35; 95% CI, 0.14–0.88; $P = .02$).

It is important to highlight that a standardized definition of TH is not available.[19] Additionally, variability exists in the methods used to assess TH, including intestinal ultrasound, MRE, and CTE.[20] In our study, to address this limitation of lacking a universally accepted definition of TH, we agreed upfront, within an investigator's meeting, on the definitions of TH and MRE response, using the most stringent definition of TH. The definition of MRE response considered that BWT might be a more difficult lesion to heal on MRE, as demonstrated in the analysis looking into the healing of individual lesions on MRE (Table 3).

In our study, the overall TH rate was 21%. Nevertheless, we observed that the early introduction of biological therapy in patients with CD increased TH rates by

Table 3. Individual Healing of MRE Lesions

	Early biologic (≤12 months from diagnosis)				Late biologic (>12 months from diagnosis)			
Variables identified	0M	12M	*P*-value	% persistent lesions	0M	12M	*P*-value	% persistent lesions
Increased BWT (>3 mm)	100 (59/59)	66 (39/59)	< .001	66 (39/59)	97 (92/95)	85 (81/95)	.002	87 (80/92)
Ulcers	37 (22/59)	15 (9/59)	< .001	36 (8/22)	54 (51/95)	33 (31/95)	< .001	55 (28/51)
Increased contrast enhancement	95 (56/59)	61 (36/59)	< .001	62 (35/56)	92 (87/95)	76 (72/95)	.002	78 (68/87)
Engorgement of the vasa recta	69 (41/59)	27 (16/59)	< .001	36 (15/41)	68 (65/96)	30 (29/95)	< .001	40 (26/65)
Peri-enteric fat stranding	52 (31/59)	24 (14/59)	< .001	39 (12/31)	56 (53/95)	32 (30/95)	< .001	43 (23/53)
Free fluid	15 (9/59)	0 (0/59)	.003	0 (0/9)	9 (9/95)	0 (0/95)	.003	0 (0/9)
Stricture	30 (18/59)	24 (14/59)	**.3**	50 (9/18)	44 (42/95)	37 (35/95)	**.07**	74 (31/42)
Penetrating lesions (fistula, sinus tract, abscess, or inflammatory mass)	27 (16/59)	12 (7/59)	.007	38 (6/16)	28 (27/95)	19 (18/95)	.01	59 (16/27)

Note: Data are presented as percentage (number/total).
Note: Bold *P* values indicate non-statistical significance.
BWT, bowel wall thickness; M, months; MRE, magnetic resonance enterography.

11 percentage points to 32%. Although MRE may have limitations in evaluating transmural inflammation in the colon due to insufficient lumen distension, our findings suggest that achieving TH might be more challenging in the small bowel and that early initiation of biological treatment could contribute to higher small bowel TH rates. Consistent with previous findings for EH,[12] our results suggest that initiating biologic therapy early and having a shorter disease duration contribute to prompt control of transmural inflammation. Importantly, patients who did not achieve TH exhibited higher rates of strictures during the baseline cross-sectional assessment (46% vs 12%; $P < .01$). This finding is particularly significant, as strictures exhibited minimal change from

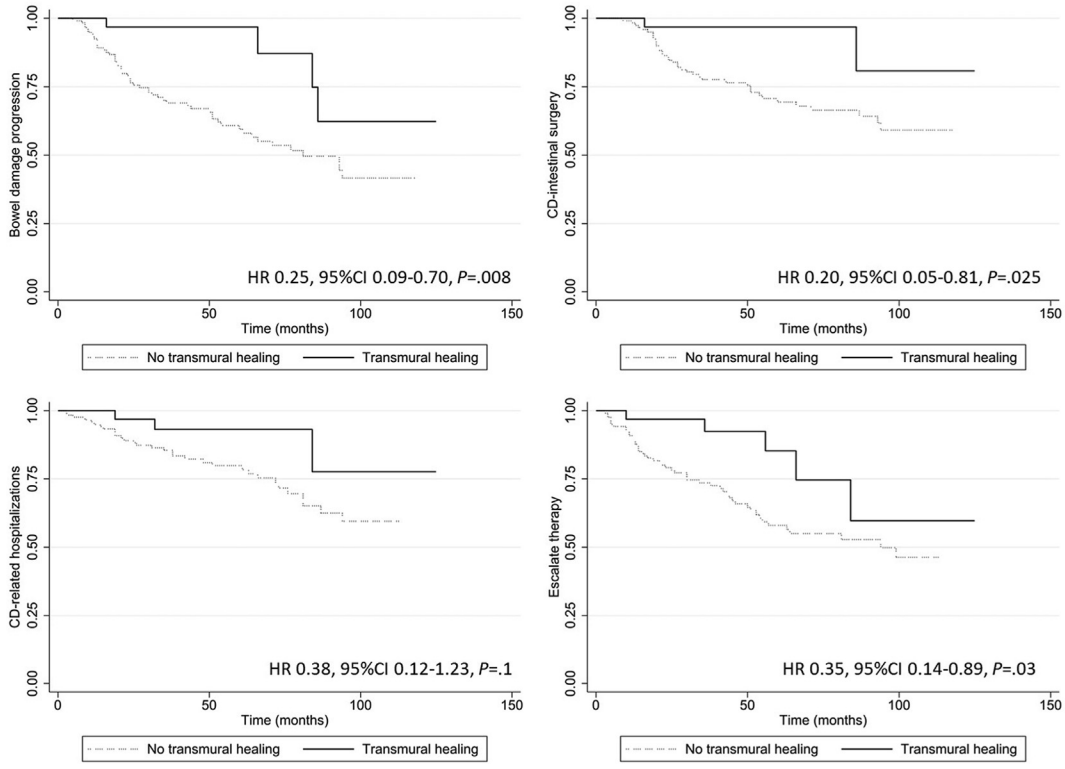


Figure 3. Kaplan-Meier curves on the role of TH in long-term outcomes.

baseline even with the introduction of biological therapy, underscoring the critical need for early inflammation control. Moreover, early biological therapy was significantly associated with MRE response, although the effect was less pronounced than TH. Early biological treatment might have a greater impact when aiming for more stringent targets, such as normalization of BWT.

The benefits of early disease control have been emphasized in a previous systematic review with individual-patient data meta-analysis of randomized controlled trials.[10] More recently, the PROFILE trial demonstrated that very early combination therapy with infliximab and an immunomodulator resulted in higher rates of surgery-free and steroid-free remission and increased endoscopic remission rates.[21] Our study contributes to this evidence by highlighting the role of early biological intervention in achieving control of transmural inflammation.

To our knowledge, this is the first study to assess the effect of the timing of biological therapy initiation on TH achievement in a considerable sample size. A previous post-hoc analysis of the VERSIFY phase III trial highlighted the impact of biological therapy on enhancing transmural inflammation improvement at 26 and 52 weeks following vedolizumab initiation.[22] Nevertheless, the mean CD duration in this study was 12.0 years (standard deviation, 9.7 years) and 10.8 years (standard deviation, 7.3 years) for the population assessed at 26 and 52 weeks, respectively.

In our study, we employed a multidisciplinary approach, involving gastroenterologists and radiologists in an individualized and blinded assessment of clinical and radiological variables. Moreover, all examinations underwent review by expert radiologists on IBD, and our study established a practical definition for assessing TH using MRE, skipping the need for scoring systems. Furthermore, it enabled the formulation of a specific criterion for early biological treatment initiation concerning TH outcomes after one year of therapy.

Nonetheless, our study has limitations, including its retrospective design, which may introduce information bias and missing data. Additionally, local assessment of radiological exams without central reading could result in discrepancies in TH evaluation. However, we aimed to mitigate this limitation by prior consensus on the definition of TH and characterization of individual lesions. The inclusion of patients with prior biological therapy use could potentially impact the definition of early biological treatment. However, it is noteworthy that this prior biological use occurred within the first 12 months from diagnosis, suggesting that despite potentially representing a more refractory patient subset, early biological therapy remains beneficial. Additionally, we conducted a separate analysis for biologic-naïve patients, which consistently showed an association between early biological treatment initiation and higher TH rates after 1 year of therapy. Finally, although we fell short of our intended sample size of 160 patients, we were able to include 154 patients. Considering this sample size, along with the observed prevalence of TH rate in our population (21%), the allocation ratio of the population wherein only 38% initiated early biological treatment, and the OR of 3 for TH achievement in patients initiated on biological therapy within 1 year following diagnosis, we calculated a study power of 86%.

Despite these limitations, our study contributes valuable insights into the association between early biological therapy initiation and TH achievement in CD management, offering potential avenues for improving patient outcomes.

Conclusion

Our findings underscore the significance of initiating biological treatment within the first year of diagnosis for achieving higher TH rates. This early intervention is associated with lower risk of bowel damage progression, CD-intestinal surgery, and therapy escalation. These results emphasize the importance of timely therapeutic interventions in improving patient outcomes and minimizing disease progression in CD.

Supplementary Material

Note: To access the supplementary material 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.2024.07.034.

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Conflicts of interest
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Data Availability
The data, analytic methods, and study materials can be made available to other researchers upon reasonable request.

Supplementary Table 1. Baseline Characteristics According to Early and Late Biological Therapy Initiation

	Early biological therapy (38%; n = 59)	Late biological therapy (62%; n = 95)	*P*-value
Age at diagnosis, *years*	28 (22–45)	25 (19–30)	**.04**
Male gender	44 (26)	52 (49)	.3
Disease duration until biological initiation, *months*	4 (1–9)	104 (38–205)	**< .01**
Disease location			.4
Ileal (L1)	57.6 (34)	47.4 (45)	
Colonic (L2)	3.4 (2)	6.3 (6)	
Ileo-colonic (L3)	39.0 (23)	46.3 (44)	
Upper GI involvement (L4)	10 (6)	10 (9)	.9
Disease behavior			.6
Inflammatory (B1)	53 (31)	44 (42)	
Stricturing (B2)	27 (16)	33 (31)	
Fistulizing (B3)	20 (12)	23 (22)	
Perianal disease	27 (16)	32 (30)	.6
Smoking	38 (22)	35 (33)	.7
Endoscopic evaluation (maximum 3 months before biologic)			
Deep ulcers	40 (17)	34 (19)	.5
Large ulcers	29 (12)	18 (10)	.2
Strictures	42 (18)	47 (27)	.6
Cross-sectional imaging at baseline			
Extension of disease, *mm*	75 (30–180)	100 (38–150)	.5
BWT most affected segment, *mm*	7 (6–10)	8 (6–9)	1.0
Increased contrast enhancement	95 (56)	92 (87)	.4
Engorgement of the vasa recta	69 (41)	68 (65)	.9
Perienteric fat stranding	53 (31)	56 (53)	.7
Perienteric free fluid	15 (9)	9 (9)	.3
Stricture	31 (18)	44 (42)	.09
Penetrating disease	27 (16)	28 (27)	.9
Biologic started			.2
Infliximab	63 (37)	50 (48)	
Adalimumab	34 (20)	37 (35)	
Vedolizumab	0 (0)	1 (1)	
Ustekinumab	3 (2)	12 (11)	
Biologic-naïve	98 (58)	67 (64)[a]	**< .01**
Concomitant thiopurines	59 (35)	66 (63)	.4

Note: Data are presented as percentage (number) or median (interquartile range).
Note: Bold *P* values indicate statistical significance.
BWT, Bowel wall thickness; GI, gastrointestinal.
[a]Previous exposure to a biological treatment, but that was started more than 12 months following the diagnosis.

Supplementary Table 2. Cox Regression Analysis of the Impact of Persistent Individual MRE Lesions on Long-term Outcomes

	Outcomes (Cox regression analysis) HR (95% CI), *p-value*			
Persistent MRE lesions	Bowel damage progression (37%; n = 57)	CD-related surgery (26%; n = 40)	CD-flare hospitalization (23%; n = 35)	Therapy escalation (35%; n = 54)
Increased bowel wall thickening (>3 mm)	**3.8 (1.4–1 .6); *P* = .01**	**4.9 (1.2–2 .6); *P* = .03**	3.9 (0.9–16.5); *P* = .06	**2.6 (1.06–6.7); *P* = .04**
Ulcers	1.7 (0.9–3.2); *P* = .1	1.8 (0.8–3.8); *P* = .1	1.4 (0.6–3.2); *P* = .4	1.8 (0.9–3.7); *P* = .09
Increased contrast enhancement	**3.4 (1.5–7.5); *P* < .01**	**5.1 (1.6–16.6); *P* < .01**	**3.1 (1.1–8.8); *P* = .03**	**2.2 (1.1–4.6); *P* = .03**
Engorgment of the vasa recta	1.4 (0.8–2.7); *P* = .3	1.6 (0.7–3.4); *P* = .2	2.0 (0.8–4.9); *P* = .1	**3.0 (1.5–6.0); *P* < .01**
Perienteric fat stranding	1.3 (0.7–2.7); *P* = .4	1.4 (0.6–3.4); *P* = .4	2.3 (0.9–6.0); *P* = .1	**2.3 (1.1–4.8); *P* = .03**
Stricture	2.1 (0.9–4.8); *P* = .08	2.6 (0.9–7.8); *P* = .09	.8 (0.3–2.4); *P* = .8	1.3 (0.5–3.4); *P* = .5
Penetrating lesions (fistula, sinus tract, abscess, or inflammatory mass)	1.8 (0.7–4.3); *P* = .2	**3.9 (1.2–12.1); *P* = .02**	**3.4 (1.1–1 .8); *P* = .03**	**5.0 (1.3–18.5); *P* = .02**

Note: Bold values indicate statistical significance.
CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; MRE, magnetic resonance enterography.