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Transmural Healing Evaluated by Intestinal Ultrasound in Patients with Crohn's Disease Treated with Infliximab

Zicheng Huang[1,2], Wenjie Cheng[2,3*]

[1]Department of Gastroenterology, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China
[2]Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China
[3]Departments of Medical Ultrasonics, The Sixth Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China
Email: *chengwj8@mail.sysu.edu.cn

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Abstract

Background and Aims: Transmural healing (TH) has been recently proposed as a measure of deep remission in Crohn's disease (CD). This study aimed to explore the rate of TH evaluated by intestinal ultrasound (IUS) in patients with CD treated with infliximab (IFX) and its predictive value for long-time clinical remission. **Methods:** Sixty-four consecutive active CD patients prescribed IFX were retrospectively recruited and followed for at least 2 years. Patients underwent IUS evaluation including bowel wall thickness, stratification, vascularity and mesenteric fat alteration at baseline and 14 weeks after IFX initiation. TH (normalization of all IUS parameters) was assessed at 14 weeks. **Results:** Fifteen (23.4%) patients achieved TH at 14 weeks, who were at lower risk of clinical relapse during the maintenance period than patients without TH [relative risk (RR) 0.132, P = 0.020]. The multivariate analysis indicated that TH (RR = 0.076, 95% CI: 0.007 - 0.773, P = 0.029) at 14 weeks were negative independent predictors of clinical relapse for patients who achieved steroid-free CR after the induction period. Patients with serum IFX trough levels >3 ug/ml were more likely to achieve TH at 14 weeks (34.3% vs. 10.7%, P = 0.029). **Conclusion:** IUS is useful in assessing TH, which predicts long-term clinical remission in patients with CD prescribed infliximab.

Keywords

Crohn's Disease, Infliximab, Trasmural Healing, Intestinal Ultrasound

1. Introduction

Crohn's disease (CD) is idiopathic, disabling, progressive and chronic inflam-

matory disease [1]. It can affect any part of the gastrointestinal tract and is usually characterized by persistent transmural inflammation, which can consequently damage bowel structure and lead to intestinal complications [2] [3]. Transmural healing (TH), characterized as the vanishment of transmural and extramural disease-related alterations, has been recently proposed as a measure of remission depth. [4] Several studies have shown that TH was achieved in about a quarter of CD patients treated with anti-tumor necrosis factor (anti-TNF) alpha agents and was a predictor for better clinical outcomes [5]-[11]. But only a few of those studies evaluated TH by IUS [5] [6] [7] [8]. Among cross-sectional modalities, IUS has the advantages of noninvasiveness, no radiation, repeatability, general availability and low costs. Sonographic TH was generally defined as bowel wall thickness (BWT) ≤ 3 mm in any segments, with normal stratification, absence of bowel wall vascularity and mesenteric fat alteration [12] [13]. To our knowledge, TH evaluated by IUS in CD patients treated with anti-TNF alpha agents after the induction period (at 14 weeks) and its predictive value for clinical outcomes has been explored in a limited number of data [8] [14] [15].

Therefore, the aim of our study was to evaluate the rate of sonographic TH in active CD patients treated with infliximab (IFX) after the induction period (at 14 weeks) and explore its predictive value for long-time clinical remission.

2. Methods

2.1. Study Design and Patients

This was a retrospective, longitudinal cohort study at a single tertiary hospital in China. The study was approved by the Ethics Committee of the Sixth Affiliated Hospital of Sun Yat-sen University. We recruited consecutive CD patients at the Sixth Affiliated Hospital of Sun Yat-sen University from January 2019 to December 2019 following inclusion criteria: 1) confirmed active CD [1] with Harvey–Bradshaw index (HBI) > 4, BWT > 3 mm of any bowel segments and Simple Endoscopic Score for Crohn's Disease (SES-CD) ≥ 3; 2) prescribed IFX (5 mg/kg; 0, 2, 6, every 8 weeks) and naive to biologics; 3) examined with IUS at baseline and 14 weeks. Patients were not eligible if they had an ileocolonic stoma, bowel resection history, concomitant total enteral nutrition, corticosteroids, and vedolizumab and ustekinumab.

The clinical data were retrospectively collected from the IBD databases in our center. The demographic data collected at baseline were sex, age, disease location and behavior. HBI score and serum C-reactive protein (CRP) levels were collected at baseline, 14 weeks and clinical relapse. Serum IFX trough levels were collected at 14 weeks.

2.2. Colonoscopy and Mucosal Healing

Almost all active CD patients prescribed IFX were performed colonoscopy at baseline and 14 weeks in our center, except those with contraindications. In our present study, only one patient did not undergo colonoscopy at 14 weeks due to

pregnancy. Endoscopic activity at baseline and 14 weeks were assessed using the Simple Endoscopic Score for Crohn's Disease (SES-CD) by reviewing endoscopic images stored in our endoscopic image storage system [1]. MH was defined as absence of ulcerations in all bowel segments (SES-CD ≤ 2) [16].

2.3. Intestinal Ultrasound and Transmural Healing

All bowel segments (including jejunum, ileum and colon) of patients were evaluated by IUS at baseline and 14 weeks. The baseline IUS was performed within 7 days prior to IFX treatment. All examinations were performed by an experienced radiologist, who had 8 years of experience in IUS. An initial detection of inflammation was performed using the low-frequency curved array transducer (frequency range 3.0 - 5.0 MHz). A detailed examination of the bowel wall and mesenteric adipose using a high-resolution linear array probe (frequency range 8.4 - 11.0 MHz) was conducted subsequently. The following information was obtained from the most affected segments (with the greatest BWT): BWT, bowel wall stratification (BWS), bowel wall vascularity, mesenteric fat alteration. At least 2 measurements of BWT were undertaken in the long axis and transvers axis respectively. Normal bowel wall stratification (BWS) is characterized by consistent visualization of at least 3 distinct wall layers. The bowel wall vascularity was assessed by power doppler US examination using the modified Limberg score [17]. The mesenteric fat alteration was defined as homogeneous, hyperechoic changes around the bowel wall. It is different in appearance from more striated, intermixed echoes of the normal mesentery. Transmural healing (TH) was defined as BWT ≤ 3 mm in any segments with normal BWS, absence of bowel wall vascularity and mesenteric fat alteration [12] [13].

2.4. Endpoints

The primary endpoint was to investigate the rate of sonographic TH and MH in active CD patients prescribed IFX at 14 weeks. The secondary endpoints were to explore the predictive value of sonographic TH and MH for long-term steroid-free clinical remission (CR). Steroid-free CR was defined as HBI ≤ 4 without treatment of systemic steroids or budesonide [1]. Clinical relapse was defined as symptom recurrence with HBI > 4 in patients who achieved CR before [1].

2.5. Statistical Analysis

Descriptive data were presented as the mean ± standard deviation or median (interquartile range), as appropriate for a normal distribution. Categorical data are presented as the number (rate). Descriptive data were compared using the Student's t-test or Mann–Whitney U-test. Categorical data were compared using the chi-squared test or Fisher's exact test. Cohen's kappa (κ) coefficient was calculated for agreement estimation. Kaplan–Meier survival curves were used to depict the proportion of patients who maintained CR after 14 weeks and strata

were compared using the log-rank test. The Cox proportional hazard models were used to explore relevant factors. Statistical comparisons were performed using the statistical package for the social sciences (SPSS) version 21.0 software for Windows (SPSS Inc., Chicago, IL, USA), and all the comparisons were made using two-sided significance levels at $P < 0.05$.

3. Results

3.1. Patient Characteristics

Seventy-four consecutive patients of CD met the inclusion criteria. Among them, 5 patients had bowel resection history, 1 patient had an ileal stoma, 2 patients had concomitant total enteral nutrition therapy, and 2 patients were lost to follow-up. As a result, the study included 64 patients for analysis. Their baseline data are shown in Table 1. After the induction period with 3 injections of IFX, 59 patients achieved steroid-free CR and entered the maintenance period, and 5 patients dropped out of the study: 3 patients were primary loss response, 1 patient was infected with pulmonary tuberculosis, and 1 patient suffered from lung cancer. In the maintenance period, 21 patients withdrew IFX: 20 patients were clinical relapse and 1 patient was pregnant. The median follow-up time of patients enrolled was 28 months (range: 3 - 36 months).

3.2. Transmural Healing and Mucosal Healing

Compared to baseline, BWT at 14 weeks was significantly decreased (6.91 ± 1.76

Table 1. Baseline patient characteristics.

	n = 64
Female sex, n (%)	15 (23.4)
Median age, years (IQR)	24 (19.5 - 30)
Median disease duration, months (IQR)	8 (3 - 30)
Disease location, n (%)	
Ileal	9 (14.1)
Colonic	9 (14.1)
Ileocolonic	46 (71.8)
Disease behavior, n (%)	
Inflammatory	55 (85.9)
Stricturing or Penetrating	9 (14.1)
Active smoking habits, n (%)	0 (0.0)
Median HBI score (IQR)	7.5 (6.0 - 9.0)
Median CRP levels, mg/L (IQR)	11.9 (1.56 - 40.55)
SES-CD, $M \pm SD$	13.77 ± 8.77

IQR, interquartile range; HBI, Harvey–Bradshaw Index; $M \pm SD$, m*ean ± standard deviation*; CRP, C-reactive protein; SES-CD, simple endoscopic score for Crohn's disease.

mm vs. 5.08 ± 2.18 mm, P < 0.001). Fifteen of 64 (23.4%) patients achieved TH at 14 weeks. Sixty-three patients had paired colonoscopies at baseline and 14 weeks, and the SES-CD was significantly decreased (13.64 ± 8.78 vs. 5.08 ± 5.85, P < 0.001). Twenty-six of 63 (41.3%) patients achieved MH at 14 weeks. TH and MH were poorly correlated (Cohen's κ = 0.476, P < 0.001). Two patients achieved TH but not MH, and 13 patients achieved MH but not TH.

3.3. Predictive Value of TH and MH at 14 Weeks for Clinical Relapse

During the maintenance period, 39/59 (66.1%) patients achieved sustained steroid-free CR. Kaplan–Meier survival analysis showed that cumulative probability of steroid-free CR in patients with TH was significantly higher than in patients without TH (RR = 0.132, 95% CI: 0.018 - 0.991, P = 0.020) (**Figure 1(a)**). Similarly, a significantly higher cumulative probability of steroid-free CR was shown in patients with MH, compared to those without MH (RR = 0.204, 95% CI: 0.059 - 0.703, P = 0.005) (**Figure 1(b)**). Furthermore, cumulative probability of steroid-free CR in patients with TH plus MH was seemingly higher than in patients with MH only (P = 0.070) (**Figure 1(c)**).

The multivariate Cox proportional hazards regression analysis indicated that TH (RR = 0.076, 95% CI: 0.007 - 0.773, P = 0.029) at 14 weeks were negative independent predictors of clinical relapse for patients achieved steroid-free CR after the induction period, adjusted for disease duration, disease location, disease behavior, CRP levels and MH (**Table 2**).

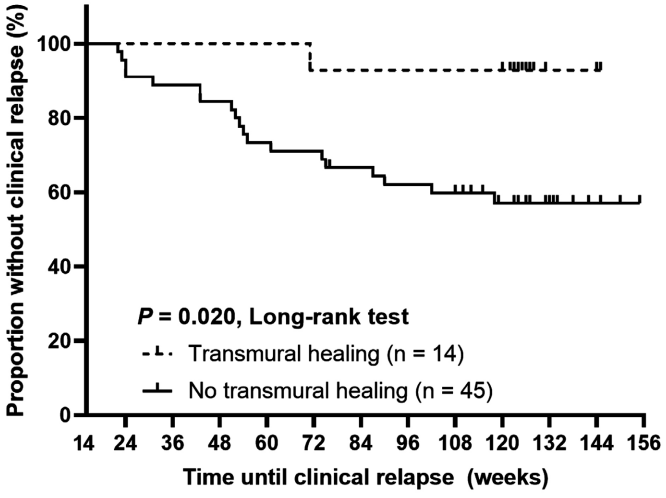
3.4. Association of Serum IFX Trough Levels and TH and MH

Sixty-three patients have measured serum IFX trough levels at 14 weeks before IFX injections: 28/63 (44.4%) patients with IFX levels ≤ 3 ug/ml and 35/63 (55.6%) patients with IFX levels > 3 ug/ml. Patients with IFX levels > 3 ug/ml were more likely to achieve TH [12/35 (34.3%) vs. 3/28 (10.7%), P = 0.029] and MH [20/35 (57.1%) vs. 5/27 (18.5%), P = 0.002] than patients with IFX levels ≤ 3 ug/ml (**Figure 2**).

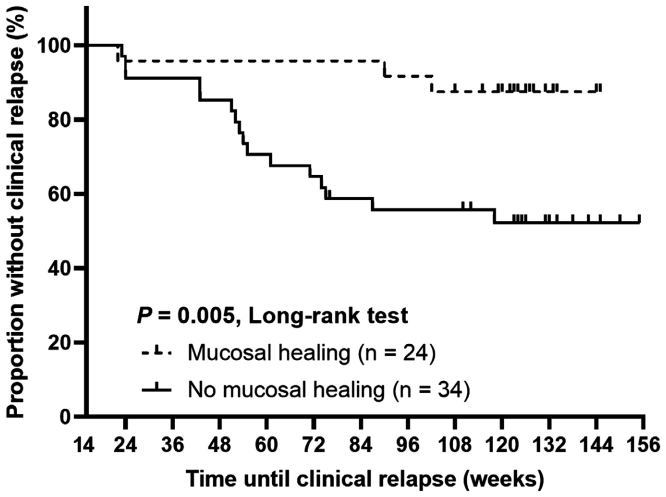
4. Discussion

This present retrospective cohort study demonstrated that 15/64 (23.4%) CD patients prescribed IFX achieved sonographic TH at 14 weeks, and had a better long-time clinical outcome during IFX maintenance therapy. Although this was a retrospective cohort study with a limited sample size, the results confirmed that sonographic TH has a good predictive value of response to IFX for patients with CD.

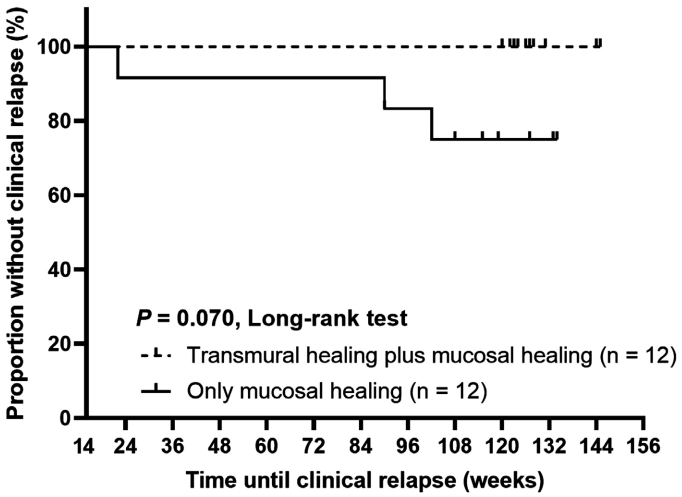
Over the past few decades, treatment goals in CD have evolved from the control of symptoms into the treat-to-target concept, and TH assessed by cross-sectional modalities such as MRE and IUS has been recently proposed as a measure of remission depth [4]. Previous studies have shown that TH was achieved in



(a)



(b)



(c)

Figure 1. Proportion without clinical relapse during infliximab maintenance period. Population in (a) (stratified by transmural healing), (b) (stratified by mucosal healing) and (c) (stratified by transmural healing plus mucosal healing) were all patients with steroid-free clinical remission at 14 weeks.

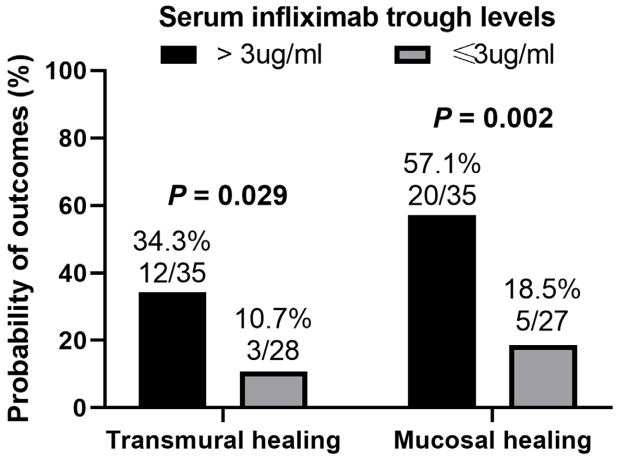


Figure 2. Percentages of patients achieving transmural healing and mucosal healing stratified by serum infliximab trough levels at 14 weeks.

Table 2. Multivariate analysis for clinical relapse of patients with steroid-free CR at 14 weeks.

Variables (reference)	RR	95% CI	*P* value
Transmural healing (without)	0.076	0.007 - 0.773	0.029
Mucosal healing (without)	0.421	0.116 - 1.526	0.188
Disease duration	1.002	0.980 - 1.025	0.848
Disease location (Ileal)	0.919	0.470 - 1.799	0.806
Disease behavior (Inflammatory)	2.803	0.870 - 9.024	0.084
CRP level (≤10 mg/L)	9.843	2.379 - 40.734	0.002

CR, clinical remission; RR, relative ratio; CI, confidence interval; CRP, C-reaction protein.

25% - 42% of CD patients prescribed anti-TNF agents, [5]-[11] which was slightly higher than the rate (23.4%) observed in our study. This discrepancy might be attributed mainly to the reason that most previous studies assessed sonographic TH in patients with treatment of anti-TNF agents for at least 1 or 2 years. [5] [6] [7] [8] [18] With patients who lost response earlier being excluded, the remaining patients might have a more stable response to anti-TNF agents than those in our study, which might overestimate the rate of sonographic TH and underestimate its predictive value of the long-time outcome. Helwig *et al.* have clearly shown that sonographic TH can be achieved in a relevant proportion of patients with CD as early as 12 weeks after standard inducing care. [13] However, to our knowledge, sonographic TH achieved by IFX therapy at 14 weeks was assessed by limited patients, and its predictive value for long-time outcomes had not been studied [15]. Our current study filled this gap and demonstrated that sonographic TH was achieved in 23.4% of CD patients prescribed IFX at 14 weeks. Patients with TH at 14 weeks sustained steroid-free CR longer than patients without, which was similar to previous studies assessing TH after 1

to 2 years of treatment with anti-TNF agents [5] [6] [7] [8] [18]. Nevertheless, it's more meaningful to detect predictors earlier in clinical practice.

Higher serum IFX trough levels have been associated with better clinical and endoscopic outcomes. [19] However, to our knowledge, data on the association between IFX levels and sonographic TH are lacking. Our current study showed patients with IFX trough levels over 3 ug/ml were more likely to achieved sonographic TH at 14 weeks. These novel findings in our study revealed that IUS assessment and therapeutic drug monitoring are complementary and associated with disease activity. Hence, we suggest that serial IUS assessment together with therapeutic drug monitoring could improve clinical outcomes of patients with CD.

Our present study has some limitations that need to be discussed. Firstly, as a single center retrospective study with a small sample size, it might have some potential bias, which needs future prospective studies with a larger sample size. Secondly, we only assessed TH in IUS and failed to perform a cross-sectional evaluation (MRE) as the reference standard. However, previous studies have demonstrated that MRE and IUS have similar diagnostic accuracy in detection of bowel lesions and disease activity [20] [21] [22]. Finally, we only evaluated IUS parameters of the most affected bowel segments, which couldn't reflect overall intestinal inflammation. It is difficult to record IUS parameters of all bowel segments by reviewing images in the retrospective study. Yet the disease activity of the most affected segments is usually the key reference for physicians to make clinical decisions.

5. Conclusion

IUS is an available and reliable tool for monitoring the response to IFX in patients with CD, and TH can be achieved in 23.4% of patients at 14 weeks, who will have a longer interval to clinical relapse. Our data also demonstrated that IFX trough level over 3 ug/ml was significantly associated with TH.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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