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Progress of Transmural Healing in Crohn's Disease

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Abstract

Recently transmural healing (TH) has become a subject of increasing interest as a potential therapeutic purpose for inflammatory bowel disease (IBD). Crohn's disease (CD) is characterized by chronic inflammation of the gastrointestinal tract, which can involve any part of the digestive tract, and the lesions are usually discontinuous, with progressive and destructive transmural lesions that can lead to irreversible damage such as fibrotic strictures, complications such as fistulas and abscesses. Disease remission remains the primary goal of therapeutic management; however transmural healing is a very promising endpoint for monitoring treatment response. Along with small bowel imaging tests such as computed tomography scans Intestinal imaging (CTE), magnetic resonance intestinal imaging (MRE), intestinal ultrasound (IUS) and other related imaging technologies are popularized in CD diagnosis and treatment benefit. Transmural healing has been initially used in clinical practice and the correlation between its rules and long-term clinical remission has been explored.

Keywords

Transmural Healing, Inflammatory Bowel Disease, Crohn's Disease

1. Introduction

Crohn's disease (CD) is a chronic transmural intestinal inflammatory disease that can involve the whole digestive tract. The development of intestinal inflammation can lead to full-thickness injury of the intestinal wall, and in severe cases, it can even cause complications such as intestinal stenosis, intestinal fistula, and abscess, thereby increasing the rate of surgical treatment in hospitalized patients and reducing the quality of life of patients [1]. Crohn's disease is char-

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acterized by transmural inflammation that may affect many different parts of the gastrointestinal tract. Approximately 25% of patients have colitis only, 25% have ileitis only, and 50% have ileocolitis. Ileocolic involvement is most commonly observed, with macroscopic thickening of the bowel wall, hypoelasticity or stiffness, and luminal narrowing [2] [3]. Traditionally, symptom relief has been considered the sole therapeutic goal for CD, but they do not take into account progressive intestinal damage and may even develop independently by the presence of symptoms [4]. Clinical assessments are subjective and poorly measurable, and in the last few years there has been increasing evidence that patients who achieve transmural healing, show better outcomes with fewer hospitalizations and surgeries and with long-term remission [5] [6] [7]. Currently, although ilocolonic examination is widely considered the reference standard for diagnosis, ilocolonic examination and histology may only assess the mucosal layer, and a combination of imaging modalities is recommended to assess for any transmural involvement and whether transmural healing has been achieved. We also confirmed the diagnosis, staged the disease, detected extracavitary complications and followed up the patients to improve the long-term remission and quality of life of the patients [3].

2. CD and Transmural Healing

2.1. Pathophysiological Mechanisms of CD

Crohn's disease appears to result from impaired interactions of commensal gut microbiota that are normally in a symbiotic state with the human host, the immune system. Metagenomic studies have shown that up to four major bacterial phyla (Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria) consist of thousands of mainly anaerobic species, they colonize the human gut in a sharp, gastric acid-driven, proximal-distal gradient [8]. Comparative studies have shown reduced clustering and diversity in patients with Crohn's disease, particularly within the Firmicutes and Bacteroidetes systems [9] [10] [11]. A decrease in Faecalibacterium prausnitzii (a Firmicute) is associated with an increased risk of postoperative recurrence of ileal Crohn's disease, and its experimental recovery has anti-inflammatory effects [12]. Crohn's disease is not caused solely by diminished symbiotic diversity, but rather requires a susceptible genotype, as suggested by mouse studies of susceptibility mutations associated with humans.

Loss of function of the epigenetic reader SP140 causes Crohn's disease, and it is not clear how improper chromatin regulation directly affects immune dysfunction in humans. Spot-protein 140 (SP140) is an immunorestricted plant homeodomain and brominated domain-containing epigenetic "reader." Loss-of-function mutations in SP140 are associated with Crohn's disease. Using a global proteomic strategy, the team of Kate L. Jeffrey of the Inflammatory Bowel Disease Center, Division of Medical Gastroenterology, Massachusetts General Hospital Research Institute, identified SP140 as a topoisomerase (TOP) repressor that maintains heterochromatin and macrophage fate [13]. The pattern recogni-

tion receptor NOD2 regulates host immunity and maintains homeostasis by sensing bacterial peptides. Loss-of-function mutations in NOD2 have been linked to Crohn's disease, but how changes in microbial factors affect NOD2 signaling and host pathology is unknown.

Hongwei Zhou's team at the Center for Microbiology, Department of Laboratory Medicine, Zhujiang Hospital, Southern Medical University, demonstrated that Firmicutes peptidoglycan remodeling enzyme, DL endopeptidase, increases NOD2 ligand levels in the gut and affects the outcome of colitis. NOD2 loss-of-function mutation is the most influential risk allele for CD, which mainly affects the risk of intestinal stricture [14]. The loss of Paneth cells and their antimicrobial granules impairs the intestinal epithelial barrier and is associated with Crohn's disease. The first line of defense of the mucosal immune system is a polarized monolayer of epithelial cells covered by mucus biofibers, secreted by goblet cells interspersed with bacteria [9]. Intraepithelial lymphocytes (IEL) are the first-line defense against infection. Identifying mediators of coordinated interactions between specific IEL and epithelial subsets could provide insights into gut barrier mechanisms in health and disease. Ken Cadwell's team at the Kilmel Center for Biology and Medicine at the Skil Bell Institute, Grossman School of Medicine, New York University, showed that a subset of IEL expressing γ- and δ T-cell receptor subunits (γδIEL) promoted the viability of Paneth cells lacking the Crohn's disease susceptibility gene ATG16L1 [15].

Intestinal fibrosis in Crohn's disease is transmural, which can erode the entire parietal tissue [16]. Studies have shown that epithelial-mesenchymal transition (EMT) is an important pathway for the origin of fibroblasts in the process of kidney, liver and intestinal fibrosis. EMT plays a large role in embryonic development, interstitial cell formation in damaged tissues, invasion and metastasis of tumors derived from epithelial cells.

Raghu Kalluri [17] can be divided into three subtypes according to the different roles played by EMT. Type I EMT is related to transplantation, embryonic development, and organ formation. Type II EMT is related to tissue regeneration and fibrosis formation after injury. Type III EMT is associated with tumor growth and metastasis. The occurrence of type II EMT is related to persistent inflammation, that is, under the continuous action of inflammation, epithelial cells break away from the epithelial layer, pass through the damaged basement membrane, accumulate in the interstitial tissue, and finally completely lose the epithelial phenotype, acquire the mesenchymal phenotype, and produce ECM (extracellular matrix). However, once the inflammatory stimulus is weakened or disappeared, the EMT process stops and organ fibrosis can be alleviated. Intestinal fibrosis is one of the characteristic manifestations of Crohn's disease, and then develops into stricture. At present, it is believed that the mechanism of intestinal fibrosis is the result of the interaction of multiple factors such as extracellular matrix (ECM), fibroblasts, cytokines and so on, which leads to excessive abnormalities. The primary [18] therapeutic goal of CD is mucosal healing, as it

is associated with long-term clinical remission and reduced surgical outcomes. However, mucosal healing does not address inflammation in the small intestine that is inaccessible to endoscopy, nor does it assess the deep tissue layers of the gut involved in developmental disease. Recent studies have shown that transmural healing (TH), defined by small bowel imaging with deep transmural healing, results in improved outcomes compared with mucosal healing alone [5] [19] [20].

2.2. Factors Affecting Transmural Healing

A combination of gene expression pathways, poor immune regulation, and altered gut microbiota has been implicated in the development of CD and stricture complications. Allison D. Ta, MD *et al.* [21], in their study, developed a predictive multivariate model to achieve TH in subgroups of patients in the Pediatric RISK study, The model is based on a centralized reanalysis of radiographic imaging from studies performed according to these recent AGA-SAR (American Gastrointestinal Association-Society for Abdominal Radiology) guidelines. They found that baseline ileal LN (lumen narrowing), increased serum albumin, and anti-yeast antibody IgG serology were all associated with subsequent TH. Multivariate regression models that included these factors had good discriminative power for TH.

There is also a link between transmural healing and biomarkers. Fabiana Castiglione *et al.* [22] demonstrated that fecal calprotectin (FC) < 94 μg/g and normal CRP were associated with TH. In earlier years, a concept of "deep remission" emerged for the treatment of CD in order to reduce structural damage and disability. It was defined as clinical and endoscopic remission [23]. The authors explored the definition of deep healing in Crohn's disease and believed that deep healing included clinical remission, mucosal healing, transmural healing, FC < 94 μg/g and normal CRP [23]. Erythrocyte sedimentation rate (ESR) was also measured in a pediatric study [19].

3. Definition and Assessment of Transmural Healing

At present, there is no unified definition and standard for transmural healing. Methods to assess transmural healing include CT Enterography (CTE), MR Enterography (MRE), and bowel ultrasonography (US) are three commonly used methods used to assess transmural healing [24]. These assessment methods are less risky, more reliable and non-invasive than endoscopic methods for assessing the prognosis of Crohn's disease. Pierre lafeuille *et al.* [5] in 154 patients with Crohn's disease, 51.9% (80/154), 10.4% (16/154), 19.5% (30/154) and 18.2% (28/154) achieved nonunion, respectively. Endoscopic mucosal healing, MRI healing, and transmural healing were observed. Transmural healing (HR = 0.05 [0.00 - 0.40], P = 0.002) and MRI healing (HR = 0.09 [0.00 - 0.47], P = 0.005) were associated with a lower risk of progression of intestinal injury compared with endoscopic mucosal healing. In addition, achieving transmural or MRI

healing, as compared with endoscopic mucosal healing, reduced the risk of the primary outcome (HR = 0.28 [0.00 - 0.74], P = 0.01). Transmural healing also reduced the risk of relapse-related drug discontinuation compared with endoscopic mucosal healing (HR = 0.35 [0.13 - 0.95], P = 0.039). Transmural and MRI healing are associated with a lower risk of progression of intestinal injury compared to endoscopic mucosal healing and can be considered better therapeutic targets for Crohn's disease.

3.1. Intestinal Ultrasonography (IUS)

There are three methods to evaluate TH, including CT enterography (CTE), MR Enterostomy (MRE) and intestinal ultrasonography (IUS) [24]. Different methods have different definitions of TH, and the definition of TH is not unified for the time being.

Intestinal ultrasound (IUS) is emerging as a key tool to achieve the therapeutic goal of transmural healing in inflammatory bowel disease (IBD). IUS is a non-invasive, radiation-free, imaging modality for IBD diagnosis and disease monitoring, including monitoring of treatment response [25]. According to a systematic review, the overall patient sensitivity and specificity of ultrasound for the diagnosis of small bowel Crohn's disease were 85% (95% CI 83% - 87%) and 98% (95% CI 95% - 99%), respectively [26]. In the evaluation of Crohn's disease, ultrasound is most accurate in the sigmoid/descending colon followed by the cecum/ascending colon and transverse colon, while the accuracy of rectal disease is poor [27]. According to the guidelines of the European Federation of Ultrasound Societies in Medicine and Biology (EFSUMB), examinations can be performed systematically with the aim of assessing the entire bowel, starting either in the lower digestive tract or in the left abdominal cavity, first assessing the sigmoid colon, then continuing along the colon to the terminal ileum, appendix, small intestine, and up to the stomach. Until now, EFSUMB guidelines have specified a bowel thickness of 2 mm, as a threshold to define normality [28]. In studies using IUS in Crohn's disease, bowel wall thickness (BWT) was considered normal in the presence of values <3 mm. Positive BS was defined as occurrence of concentric and regularly increasing BWT > 3 mm [29]. Tomas Ripolles *et al.* [30] in their study, ultrasound improvement was considered when the bowel wall thickness was ≤3 mm, in addition to color Doppler grade 0 and no complications, regardless of whether wall enhancement was persistent or not. Ultrasound improvement was considered if wall thickness decreased by ≥2 mm, color Doppler flow decreased by one grade, and mural enhancement decreased by ≥20%, and/or transmural complications or disappearance of stenosis. Finally, ultrasound improvement was not considered when ultrasound findings did not improve or worsened. Kucharzik *et al.* [31] used intestinal ultrasound to define the normal intestinal wall thickness (BWT) of all intestinal segments (≤2.0 mm terminal ileum; ≤3.0 mm colon) was TH.

Fortunata Civitelli *et al.* [32], in their study of pediatric Crohn's disease, also

used Doppler parameters to define TH. TH was defined as bowel wall (BW) thickness <3 mm. The vessels were studied with the use of color Doppler imaging at the lowest available pulse repetition rate (6.5 per sec). The presence of color signals within BW was considered to be pathologic; Loss of the normal 5-layer appearance of BW was considered abnormal; Stenosis was defined as lumen diameter of 1 cm, whereas pre-stenosis dilatation was defined as lumen 0.2.5 cm. It can be seen that there is no uniform standard for ultrasound evaluation of transmural healing, and most studies use intestinal wall thickness ≤3 mm as the standard.

Ulf Helwig *et al.* [33] used IUS to define transmural reaction and TH, and they adopted the following three different definitions of TH: simplified TH, extended TH or full TH. Simplified TH was defined as normalized BWT [CD: terminal ileum ≤2 mm, colon ≤3 mm; UC: sigmoid colon ≤4 mm, descending/ascending/transverse colon of each ≤3 mm] and color Doppler signal without magnification [Limberg 1/2 for CD, Responno for UC]. Extended TH was defined as normalized BWT and normalized color Doppler signal or no loss of stratification or no fibrofat proliferation. Among the above factors, at least BWT normalization and two additional factors must be present to meet the definition of extended TH. If all four factors are present, the TH is intact. Their experimental finding of an IUS response and a relevant proportion of patients with TH suggests that IUS is a useful method for assessing transmural inflammatory activity in daily clinical practice; TH and transmural response (TR) can predict the ultrasound results at 52 weeks.

In addition, contrast-enhanced ultrasound (CEUS) is a useful tool to characterize suspected swelling and inflammatory paralysis, as well as to confirm the route of swelling and quantify disease activity in IBD. With regard to the distinction between fibrosis and inflammatory stenosis in IBD, strong evidence suggests that CEUS, in combination with further ultrasound tools, will soon become a determinant of this distinction [34].

3.2. CT Enterography (CTE)

Abdominal CT enterography was the preferred first-line radiological examination for the evaluation of small intestinal CD, with a sensitivity of 95.2% [35]. In the studies using CTE to evaluate TH, in the study by Parakkal Deepak *et al.* [6], radiologists evaluated no segmental wall hyperenhancement and wall thickness ≤3 mm as TH in the small intestine, and comb sign, active inflammation, periintestinal inflammation, fistula and stenosis were also evaluated. In the study of Lucrezia Laterza *et al.* [36], TH was defined according to the qualitative judgment of typical CTE lesions of Crohn's disease (BWT >3 mm, stenosis, target sign, comb-like sign, lymph node enlargement >1 cm, abscess, fistula, sinus tract, fibrofatty hyperplasia, periintestinal strangulation and abdominal free fluid. In Hiroyuki Fujimura *et al.*'s experiment, CTE was used for comparison, and TH assessed by CTE was defined as the absence of excessive bowel wall en-

hancement, abnormal bowel wall thickness (≥3 mm), increased mesenteric adipose tissue concentration, and fistula or abscess [37].

3.3. MR Enterography (MRE)

Noninvasive cross-sectional imaging modalities, particularly magnetic resonance enterography (MRE), are highly sensitive and specific for detecting active transmural small bowel inflammation and complications and allow assessment of the entire small intestine (SB) [38]. Compared with CTE, MRE has the advantages of non-ionizing radiation, high soft tissue resolution and multi-sequence imaging, which shows great value in the diagnosis and efficacy evaluation of CD, and can be used as the preferred imaging method for the follow-up evaluation of CD patients [39]. The sensitivity and specificity of MRI in detecting small bowel disease were 78% (95% CI 67% - 84%) and 83% (95% CI 76% - 90%), respectively [40]. Halle *et al.* [41] used MRE to define TH as no segmental wall hyperintensity, no comber sign or lymphadenopathy, BWT ≤ 7 mm, and no complications (e.g., abscess, stenosis, or fistula) compared with normal small intestine. Rose Vaughan *et al.* [42] defined TH as BWT ≤3 mm and absence of congestion when color Doppler, inflammatory fat, or stratification of the bowel wall was interrupted. Inbar Nakar *et al.* [19] in their study of Crohn's disease in children, for MRE, they measured the radiologist's global assessment (RGA) on a visual analogue scale (0 - 100 mm) and used a cutoff value of <19.5 mm to define healing. In the experiment of Castiglione F *et al.* [29], TH defined by MRE (bowel wall thickness <3 mm without signs of vascular excess) and non-contrast enhanced bowel US (bowel wall thickness <3 mm) were used in patients receiving anti-tumor necrosis factor therapy for 2 years. Anthony Buisson *et al.* [43] defined bowel wall healing using either the Clermont score (without segmental Clermont score) or MaRIA (without segmental MaRIA). With respect to MaRIA score, the definition of TH has been proposed as a non-segmented MaRIA score > 7 or a non-segmented Clermont score > 8.4. In recent years, when clinical researchers used MRE evaluation, TH was mostly defined as the thickness of bowel wall ≤3 mm and no ulceration, edema, enhancement and complications on all segments of ileum [44] [45].

4. The Significance of Transmural Healing

In contrast to ulcerative colitis (UC), CD patients present with deep rather than superficial ulcers. Thus, although the ulcer surface is healed, some inflammatory reaction in the mucosa or bowel wall may persist. Recently, many scholars have designed experiments to confirm that transmural healing and MRI healing have a lower risk of intestinal injury progression than endoscopic mucosal healing, and can predict long-term results, which can be considered as better treatment targets for Crohn's disease [5] [46]. Eleonore Halle *et al.* [41] showed that radiological response was associated with reduced risk of surgical or endoscopic intervention, which should be considered as a therapeutic target for patients with

Crohn's disease. Sophie Gey *et al.* [47] they analyzed all intervention and non-intervention studies evaluating TH and its effect on disease-related outcomes of Crohn's disease by searching PubMed, Cochrane Library and Web of Science, and concluded that TH was associated with improved long-term outcomes of CD patients. It should be considered as a new therapeutic target. So Yoon Choi *et al.* [44] observed a significant difference in IFX TLs between the two groups of patients with and without EH in their experiments. However, there was no difference in IFX TLs (in fliximab trough levels) between the two groups of patients with and without TH. Therefore, the authors believe that TH is a further remission target than EH, and that TH patients may be a subgroup of EH patients. This article summarizes the advantages of transmural healing as a better treatment target for Crohn's disease from four aspects: shorter hospital stay, fewer operations, less intestinal injury, and longer clinical remission period.

4.1. Hospitalization Rate

Some studies have shown that transmural healing can shorten the length of hospital stay. Parakkal Deepak *et al.* [6] in their study, complete remission of CTE/MRE reduced the risk of hospitalization by more than two-thirds. Pierre Lafeuille *et al.* [5] in their cohort, transmural healing (HR = 0.11 [0.03 - 0.47], P = 0.003), MRI healing (HR = 0.35 [0.16 - 0.80], P = 0.012) and endoscopic mucosal healing (HR = 0.35 [0.12 - 0.98], P = 0.046) were associated with lower risk of subsequent hospitalization. Fabiana Castiglione *et al.* [48] observed the treatment of Crohn's disease with biological agents for one year, comparing the treatment effect of transmural healing with mucosal healing or non-healing; They found that transmural healing was associated with a higher rate of steroid-free clinical remission (95.6%) and a lower rate of hospitalization (8.8%) compared with mucosal healing (75%, 28.3%, and 10%, respectively) and nonhealing (41%, 66.6%, and 35.5%, respectively) (P < 0.001). In a 5-year clinical observational study of Samuel Raimundo Fernandes *et al.* [49], transmural healing was achieved in 20.8% of patients and found that transmural healing was associated with a lower risk of hospitalization (odds-radio (OR). 244 [0.111 - 0.538], P < 0.001).

4.2. Operation Rate

In their experimental follow-up, Pierre Lafeuille *et al.* [5] found that transmural healing and MRI healing were associated with reduced surgical risk compared with non-healing patients. Cary G. Sauer *et al.* [50] confirmed that in pediatric patients, patients who achieved transmural healing had a significantly lower rate of CD-related surgery than those who did not. SamuelRaimundo Fernandes *et al.* found that patients who achieved transmural healing had a lower surgical risk (odds ratio (OR). 132 [0.030 - 0.585], P = 0.008) [49]. Fabiana Castiglione *et al.* [48] compared with mucosal healing (75%, 28.3% and 10%, respectively) and non-healing (41%, 66.6% and 35.5%, respectively) (P < 0.001), Transmural heal-

ing was associated with a higher steroid-free clinical remission rate (95.6%) at 1 year and a lower need for surgery (0%).

4.3. Process of Intestinal Injury

Pierre Lafeuille *et al.* [5] in their study showed that in univariate analysis, transmural healing and MRI healing had a lower risk of intestinal injury progression compared with non-healing and endoscopic mucosal healing. In the experiment of L. Messadeg *et al.* [51], it was found that MRI assessment of early transmutinal response at 12 weeks after the initiation of anti-tumor necrosis factor therapy in CD patients could prevent the progression of intestinal injury and predict the sustained clinical remission of patients.

4.4. Patients Who Achieved Transmural Healing Criteria Had Longer Periods of Clinical Remission

Eder *et al.* [7] showed that adult CD patients who achieved transmural healing 1 year after drug withdrawal had a longer average clinical remission time of CD than those who did not achieve transmural healing (45 months vs 18 months, P = 0.02). Ripolles *et al.* [30] showed that adult CD patients who achieved transmural healing had a higher clinical remission rate of CD within one year than the control group. Sauer *et al.* [52] found that the clinical remission rate of CD in children with transmural healing was higher than that in children without transmural healing. Piotr Eder *et al.* [53] found that TH was significantly associated with a good treatment outcome (p = 0.02) at a median follow-up (29 months), with 75% (IQR: 35% - 97%) sensitivity and 72% (IQR: 46% - 90%) specificity in predicting long-term remission.

5. The Latest Clinical Research on Transmural Healing of CD

In contrast to ulcerative colitis (UC), CD patients present with deep rather than superficial ulcers. Thus, although the ulcer surface is healed, some inflammatory reaction in the mucosa or bowel wall may persist. In recent years, many researchers have designed experiments to confirm that transmural healing and MRI healing have a lower risk of intestinal injury progression and can predict a longer-term outcome than endoscopic mucosal healing, which can be considered as a better therapeutic target for Crohn's disease [5] [46]. Eleonore Halle *et al.* [41] showed that radiological response was associated with a reduced risk of surgical or endoscopic intervention and should be considered as a therapeutic target for patients with Crohn's disease. Sophie Gey *et al.* [47] they analyzed all intervention and non-intervention studies evaluating TH and its effect on disease-related outcomes of Crohn's disease by searching PubMed, Cochrane Library and Web of Science, and concluded that TH was associated with improved long-term outcomes of CD patients. It should be considered as a new therapeutic target. So Yoon Choi [44] *et al.* observed a significant difference in IFX TLs between the two groups of patients with and without EH in their experiments.

However, there was no difference in IFX TLs (in fliximab trough levels) between the two groups of patients with and without TH. Therefore, the authors believe that TH is a further remission target than EH, and that TH patients may be a subgroup of EH patients. Compared with mucosal healing, transmural healing can achieve better prognosis from four aspects: shorter hospital stay [5] [6] [48], fewer operations [5] [50], less intestinal injury [51], and longer clinical remission period [7] [52] [53]. Transmural healing can be considered a better therapeutic target for Crohn's disease.

In recent years, transmural healing has gradually become one of the criteria for CD healing, and more and more scholars and experts have applied it to clinical observation. The study by Jose Maria Paredes *et al.* [54] found that patients who achieved transmural healing under intestinal ultrasound after anti-tumor necrosis factor-α antibody (anti-TNF) treatment had better clinical outcomes. During the follow-up (median 48.5 months), 23 of the 33 (69.7%) patients in remission or response after induction therapy presented a good outcome. Sonographic TH was significantly related with better outcomes, with only 1/14 patients having a poor outcome compared to 9/19 without TH (OR 11.7, 95% CI 1.2 - 108.2 P = 0.01, Chi-squared test). Fortunata Civitelli, MD, PhD *et al.* [32] treating pediatric Crohn's disease with anti-tumor necrosis factor-*α* found that transmucular inflammation also improved during treatment, but complete TH was achieved in only a small proportion of patients. Fabiana Castiglione *et al.* [20] their study included 66 CD patients treated with biologics and 67 patients treated with thiopurines. As a result, 17 patients treated with biologics developed TH, of which only 3 were treated with thiopurines. They found that TH could be achieved in about 25% of CD patients treated with anti-Tnf-*α* drugs and was significantly associated with MH.

Some scholars use transmural healing and study the best time for drugs to achieve transmural healing in order to master the rules of medication. In the study of the relationship between the duration of infliximab (IFX) treatment and the achieving transmural healing, Huang Zichong *et al.* [55] found that at the 14th week, the BWT of the early treatment group decreased [3.0 (1.3, 3.0) mm vs. 1.0 (0,2.0) mm, Z = -2.922, P < 0.05]. P = 0.003), transmural healing rate (39.3% (11/28) vs. 11.5% (3/26), χ^2 = 5.405, P = 0.020) and mucosal healing rate (52.2% (12/23) vs. 20.8% (5/24), χ^2 = 4.997, P = 0.020). P = 0.025] were higher than those in the late treatment group, and the differences were statistically significant. However, it has also been shown that transmural thickness ≥4 mm can predict subsequent treatment failure in CD patients treated with IFX, suggesting that transmural thickness <4 mm is a potentially new valuable therapeutic target [56].

T. Kucharzik *et al.* [31] in this international, interventional, multicenter study of usturocuzumab (UST) in the treatment of CD and the use of IUS to evaluate it, found that the improvement in BWT at baseline was statistically significant at W4 (P = 0.0002), and BWT and Doppler signals began to normalize at W8. And

11.3% of patients achieved transmural healing at W16, mainly in the colon. The clinical trial of Longyuan Zhou *et al.* [45] found that nearly one-fifth of patients observed early TH assessed by MRE at week 26 of ustekinumab (UST) treatment; The apparent diffusion coefficient (ADC), one of the parameters of MRE evaluated, may positively predict early TH.

Evaluation by J. Reves *et al.* found that early biological introduction of therapy, defined as <12 months after definitive diagnosis, was significantly associated with an increased probability of TH [57]. They included 168 patients (51% females), with a median age at diagnosis of 25 years old (IQR 19 - 34). In the multivariate logistic regression model, early initiation of biological treatment was significantly associated with increased probability of achieving CR (OR 4.3, 95%CI 1.6 - 11.5, P = 0.003), ER (OR 2.9, 95%CI 1.2 - 7.1, P = 0.02) and TH (OR 2.7, 95%CI 1.002 - 7.1, P = 0.049). By comparing patients with early and late biotherapy (defined as ≤12 months versus >12 months after diagnosis) in a single-center retrospective cohort study, their clinical trial found that early biotherapy seemed to be independently associated with higher transmural healing rates, further increasing the relevance of early intervention in CD [15].

When studying the efficacy of oral total enteral nutrition (EEN) in inducing mucosal and transmembrane healing in CD patients, Jia-Min Chen *et al.* [58] found that oral EEN treatment was very effective in inducing mucosal healing in CD patients, although only 5 patients (17%) achieved transmural healing. However, a significant reduction in bowel wall thickness was observed (9.416 3.06 vs 4.976 1.76 mm, P < 0.001), and a significant improvement was observed in complications assessed by intestinal ultrasound (including ascites, ascites, and stenosis).

Some experts have proposed that future treatment algorithms could use the pediatric inflammatory Crohn's magnetic resonance enterography index (PICMI) or the PICMI-based, validated IUS score to measure long-term transmural healing. The development of PICMI, an accurate and reliable indicator for monitoring transmembrane disease activity in children, has the potential to influence pediatric CD surveillance algorithms. Longitudinal studies using PICMI at baseline as an early monitoring tool and ultimate therapeutic goal have the power to provide evidence on the role of transmural healing, particularly the ability to alter disease progression in children with CD compared to mucosal healing [59].

The concept of transmural healing was also introduced in the integration of traditional Chinese and western medicine. Shen Hong *et al.* [60] devoted to the treatment of Crohn's disease with integrated traditional Chinese and western medicine. Starting from the etiology and pathogenesis, the treatment can be adopted to remove dampness and remove turbidity, benefit qi and transport the spleen, detoxifying and healing ulcers, removing blood stasis and nourishing muscle to promote transmural healing. Whether traditional Chinese medicine combined with biological agents can improve the transmural healing rate of patients is one of the fields worth exploring.

6. Summary and Prospect

6.1. Summary

The treatment goal of Crohn's disease has evolved from clinical remission to endoscopic remission, to histological remission, and now to transmural healing. As a disease involving the whole intestinal wall, MH under endoscopy and histological remission alone cannot represent the true remission of CD. In recent years, several studies have shown that transmural healing is associated with better prognosis of CD, and there are more data to support TH as a therapeutic target for CD. However, there is no unified definition and scoring standard for TH. The most widely used definition of TH is BTW < 3 mm. TH has been used as the ultimate therapeutic target for Crohn's disease in clinical observational trials to further understand the timing of medication. The goal of researchers is to reduce the hospitalization rate, operation rate, the process of intestinal injury, and improve the quality of life of patients.

6.2. Outlook

TH is associated with a better long-term prognosis of Crohn's disease, which has become a new target and end point in the treatment of Crohn's disease, and is expected to guide clinical treatment to achieve a better prognosis and improve the life of patients. It is necessary to achieve transmural healing, but there is no unified definition and scoring standard for TH, which is still the most important problem for researchers.

Conflicts of Interest

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

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