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Editorial Board Member of *World Journal of Clinical Cases*, Ashu Seith Bhalla, MD, Professor, Department of Radiodiagnosis, All India Institute of Medical Sciences, New Delhi 110029, India

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Baishideng Publishing Group Inc
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Telephone: +1-925-2238242
Fax: +1-925-2238243
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REVIEW

Treat-to-target in Crohn's disease: Will transmural healing become a therapeutic endpoint?

Elena Daniela Serban

Elena Daniela Serban, 2nd Department of Pediatrics, "Iuliu Hatieganu" University of Medicine and Pharmacy, Emergency Hospital for Children, Cluj-Napoca 400177, Romania

ORCID number: Elena Daniela Serban (0000-0003-0906-1232).

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Correspondence to: Elena Daniela Serban, MD, PhD, Associate Professor, Pediatric Gastroenterologist, 2nd Department of Pediatrics, "Iuliu Hatieganu" University of Medicine and Pharmacy, Emergency Hospital for Children, 5 Crisan Street, Cluj-Napoca 400177,
Romania. daniela.serban@umfcluj.ro
Telephone: +40-264-532216
Fax: +40-264-590478

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Abstract

Crohn's disease (CD) represents a chronic transmural inflammatory condition of the gastrointestinal tract, which usually leads to structural damage and significant disability. Deep remission - defined by both clinical and endoscopic remission, signifying mucosal healing - represents the current endpoint in the treat-to-target strategy, significantly improving patients' long-term outcomes. Transmural healing (TH) could be a more effective target, but this possibility remains unclear. This narrative review aims to critically review and summarize the available literature relating TH to long-term outcomes, being the first of its kind and to the best of the author's knowledge. A systematic literature search (from inception to March 31 2018) was performed, using multiple databases, and identifying seven full-text manuscripts. In those studies, long-term favorable outcomes ($\geqslant$ 52 wk) included sustained clinical remission, as well as fewer therapeutic changes, CD-related hospitalizations, and surgeries. Despite heterogeneous design and methodological limitations, six of the studies demonstrated that TH or intestinal healing (TH plus mucosal healing) were predictive for the aforementioned favorable outcomes. Therefore, TH may become a reasonable therapeutic target and be included in the concept of deep remission. Further prospective, well-designed, multicenter trials aiming to better define the role of TH in personalized therapy for CD and to determine the long-term influence of TH on bowel damage and disability are warranted.

Key words: Treat to target; Cross sectional imaging; Deep remission; Transmural healing; Intestinal healing; Long-term outcomes; Bowel damage; Crohn's disease

Core tip: Crohn's disease (CD) represents a chronic transmural inflammatory condition of the gastrointes-

tinal tract, potentially leading to structural damage and disability. Deep remission (clinical and endoscopic remission), the current therapeutic goal, significantly improves patients' long-term outcomes. Transmural healing (TH) could be a more effective target. Therefore, this narrative review (the first of its kind, to the best of the author's knowledge) aims to provide the currently available scientific evidence on the predictive role of TH for long-term outcomes (clinical remission, therapeutic changes, CD-related hospitalizations and surgeries) and to establish whether TH should become a therapeutic endpoint in the treat-to-target strategy.

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INTRODUCTION

Crohn's disease (CD) represents a chronic transmural inflammatory condition of the gastrointestinal tract, that could lead to structural damage and significant disability[1-5]. Therefore, it is crucial to initiate the most effective therapy in a timely manner (in the so-called "window of opportunity"), in order to prevent bowel damage (BD; *i.e.,* complications like strictures, fistulae, and abscesses) requiring surgery, leading to further disability and poorer quality of life[6,7]. According to the concept of "treat-to-target" strategy (STRIDE), deep remission (DR) has become the new therapeutic goal[8]. DR includes clinical (steroid-free)/patient-reported outcome remission (defined as resolution of abdominal pain and diarrhea/altered bowel habit) and endoscopic remission [*i.e.*, mucosal healing (MH), defined as resolution of ulceration at ileocolonoscopy (IC)], or resolution of findings of inflammation on cross-sectional imaging (CSI) in patients who cannot be adequately assessed with IC[8].

Systematic reviews and meta-analyses of both cohort studies and randomized controlled trials have demonstrated that MH (part of DR) assessed by IC was a strong predictor for better outcomes, including sustained long-term steroid-free clinical remission (CR) and MH as well as lower rates of CD-related hospitalizations and surgeries[9,10]. However, over the last few years, researchers have questioned whether MH is a sufficient endpoint, given that CD represents a transmural disease and active intramural inflammation and that damage can persist despite the presence of MH at endoscopy[11-17]. It was suggested that the more inclusive "bowel healing" or "deep healing" (referred to as "IH" and describing healing of the whole intestinal wall) may be a more appropriate therapeutic goal than MH[9,13,18].

The concept of transmural healing (TH) evaluated by CSI was developed several years ago and regarded as a logical goal of treatment, both in adult[19] and pediatric patients[20,21] with CD; however, reliable definitions of TH were not available at that time. Castiglione *et al*[22] were among the first to define and highlight the concept of TH as a bowel wall thickness (BWT) of < 3 mm assessed by bowel ultrasonography (US). The authors also reported that TH was reached in 25% of adults with CD who were treated with anti-tumor necrosis factor alpha (TNF) agents for 2 year[22]. Since then, the achievement of TH under certain therapeutic approaches has become a subject of growing interest, in both children and adults. More than 20 recent studies have revealed that therapeutic response is associated with improvements, including TH, detected at CSI. Imaging techniques used in these studies included magnetic resonance enterography or enteroclysis (MRE)[23-32], US [Doppler[22,32-35] or with contrast agents (contrast-enhanced US, commonly known as CEUS[36], or small intestine contrast US, commonly known as SICUS[11,12]) and computed tomography enterography or enteroclysis (CTE)][37-40]. The demonstrated rates of TH under various medications range from 0% (after 2 wk[24] and even 12 mo[11,39]) to 14% (after 1 year)[12] and as high as 25% (after 2 year)[32]. However, no unanimous definition of TH was used in these studies.

Most series have found a good significant correlation between TH and MH[22,26,28-32,36], while other researchers found agreement with endoscopy only for some parameters, mainly extramural[40], and others did not find any agreement between CSI and IC improvements[11,12,37]. Among the last category, one study reported that 27% of patients with complete MH showed evidence of transmural inflammation[12]. TH, therefore, likely reflects a deeper level of healing, which could be correlated with a more stable and long lasting CR[18]. However, none of the aforementioned studies was designed to analyze the benefits of achieving TH on patients' long-term outcomes.

Recent interesting studies have included radiological response/TH under therapy as a treatment endpoint and related it to long-term outcomes[13,14,41], showing significant benefits of achieving TH *vs* persistent active transmural inflammation. TH could become a therapeutic goal, but only if it has been constantly demonstrated to improve patients' long-term outcomes (*i.e.,* sustained CR, fewer therapeutic changes, CD-related hospitalizations and surgeries, and reduction of BD and of disability). Therefore, the aim of this narrative review is to provide the currently available scientific evidence on the predictive role of TH in CD for long-term outcomes, in order to establish whether TH should become a therapeutic endpoint in the "treat-to-target" strategy.

LITERATURE SEARCH

Database searches

Published full-text manuscripts were identified from inception to March 31 2018 by a systematic literature

search of MEDLINE (PubMed), EMBASE, The Cochrane Library, Web of Science, Google Scholar, ResearchGate and Mendeley databases. Only articles published in the English language were included. The reference lists from the selected studies were manually examined to identify additional research studies. Duplicates were excluded. The search included the following items/key words: ("Crohn's disease", "inflammatory bowel disease") and ("transmural healing", "transmural remission", "deep healing", "bowel healing", "gut healing", "intestinal healing", "parietal healing", "radiological remission", "radiological healing") and ("cross-sectional imaging", "magnetic resonance imaging", "magnetic resonance enterography", "magnetic resonance enteroclysis", "computed tomography enterography", "abdominal ultrasonography", "abdominal ultrasound", "color-Doppler ultrasound", "small-intestine contrast-ultrasonography", "contrast-enhanced ultrasonography") and ("outcomes"). Only studies reporting on long-term outcomes after TH (at least 12 mo), like CR and/or TH, medication changes, CD-related surgery rate and hospitalization rate, and influence on BD and disability were included.

Data extraction

The following data were extracted from each identified article: Last name of the first author; publication year; country; study design; characteristics of the included population, specifically sample size, age at inclusion, sex, behavior and location of CD, previous CD-related surgery, duration of the disease, and medication; aim of the study; follow-up time; definition of CR and endoscopic MH; type of CSI used and included parameters; definition of TH and rate of achieved TH; correlation between TH and endoscopic MH; long-term CR and TH; change in medication; CD-related hospitalization; CD-related surgery; influence of TH on BD and disability; potential limits of the studies; and, any other relevant data regarding TH.

TRANSMURAL HEALING

Characteristics of included studies

Seven full manuscripts, all published in 2016 or 2017, were included, with heterogeneous design. The main characteristics of these studies are detailed in Table 1[13-15,41-44]. Three studies were prospective[15,41,44] and four were retrospective[13,14,42,43]. Only one study was performed in children[43]. The size of the study population ranged from 26[42] to 214[13] patients. Location of CD, defined by Montreal[45] or Paris[46] classification was as follows: ileocolon (L3)[42]; terminal ileum (± caecum) (L1) and ileocolon (L3)[13,14,44]; and, all types of location (L1, L2, L3 ± L4)[15,41,43]. Patients presented all types of CD behavior (defined by Montreal[45] or Paris[46] classification), the most prominent being inflammatory behavior (B1)[13,14,41-44]. Prior CD-related surgery was mentioned in five studies[13-15,41,44] and its rate ranged from 22.8%[15] to 61.3%[14]. All studies mentioned the duration of the disease, with the lowest median being 4 year[42] and the highest median being 9 year[14]. Three studies included only patients treated with anti-TNF agents, either as monotherapy or combined with other medication[41,42,44], while in other studies patients were on various therapies[13-15,43]. The following CSI were used: MRE[13,42,43]; MRE and CTE[14]; US and CEUS[41]; US and US elastography[44]; and, CTE[15]. Timing of CSI performance varied among the studies, representing at inclusion in the study[13,15], at a certain point after diagnosis[43], before and after anti-TNF induction[42], pre-therapy and after 6 mo or two examinations given $\geqslant$ 6 mo apart[14], and at baseline, after induction, and after 1 year of treatment[41,44].

Various definitions/scoring systems were used to describe the CR, MH and radiological remission/TH, as detailed in Table 2. CR was considered in four studies[15,41-43], two of which did not use IC[41,43]. MH was defined at IC in four studies[13-15,42]. Regarding CSI, various definitions of TH were used, according to several scores and parameters, as detailed in Table 2. Two studies also included IH[13,42], assessed by colonoscopy and MRE. In studies where TH was available only at baseline (for evaluation as a predictor for outcomes), the percentage of TH varied between 17.5%[15] and 35.6%[43]. IH at inclusion was detected in 15.4%[13]. After induction therapy with anti-TNF agents, TH was detected in 14%[41], 27%[44] and 38%[42] and IH was present in 31%[42]. After at least 6 mo of various therapies, TH was achieved in 37%[14]. After 12 mo of anti-TNF therapy, TH was detected in 30%[41,44].

In studies which compared MH (at IC) and TH (evaluated by CSI), no good agreement was detected[13,15] (Table 2). In addition, one study showed that nearly one in two patients with a normal terminal ileum (at IC) had evidence of active disease (at MRE/CTE) either in the terminal ileum or proximal to it[14]. Of those with MH, TH was detected in 27% (at CTE)[15] and 54% (at MRE/CTE)[14].

Transmural healing and long-term outcomes

The included studies are detailed in Table 3.

Long-term CR: Eder *et al*[42] found that IH (achieved after induction therapy) was significant in predicting long-term CR. Median duration of CR among long-responders was 45 mo *vs* those with relapse (18 mo, P = 0.02). Moreover, lack of IH (even if CR, MH or TH were achieved) had 90% probability of exacerbation shortly after stopping 1 year of anti-TNF therapy[42]. Ripollés *et al*[41] showed that sonographic response after 12 wk of anti-TNF (induction) was more pronounced than during maintenance treatment and predicted good response at 1 year with a sensitivity and specificity of 75.9% and 81.8%, respectively, with an odds ratio of 14.14. A good sonographic response at 52 wk significantly predicted good long-term clinical outcome[41]. In children, long-term CR was significantly higher for those with TH *vs*

Table 1 Characteristics of the included studies

First author, year, country	Study type	CD population, disease location, behavior, surgery	Duration of CD in yr	MD	Aim of study	Methods used to assess CD activity, timing	Follow-up time
Eder, 2016, Czech Republic[42]	RS	26 adults, responsive to induction doses of anti-TNF, median age (IQR) 27 yr (IQR: 21-36), 61% F, L3, B1 62%, B2 7%, B3 31%	Median (IQR): 4 (2-6)	Study MD: IFX or ADA, 1 yr Concomitant MD: CS 88%, AZA 88%, 5ASA 100%, AB 54%	Predictive role of MH, TH and IH healing on long-term CR	Clinical, endoscopic, and MRE activity: before starting anti-TNF and after induction (week 12-14 for ADA and week 9-12 for IFX)	Median 29 mo (IQR: 14-46) after finishing 1 yr of anti-TNF
Sauer, 2016, United States[43]	RS	101 children, 41.6% F, L1 28%, L2 24%, L3 54.5%, L4a 17.8%, L4b 24.7%, B1 76%, B2 18%, B3 2%, B2B3 4%, perianal 14%	Median (range): 4.7 (1.65-11.5)	IMD 33%, Biologic 67%	Predictive role of MRE remission on long-term CR, MD change and surgery	MRE, at median of 1.3 yr from diagnosis	Median 2.8 yr after MRE
Deepak, 2016, United States[14]	RS	150 adults, 66% treatment-naïve, median age (IQR) at diagnosis 23 yr (IQR: 19-33), 50% F, L1 48.7%, L3 40.7%, L4 10.6%, B1 45%, B2 35.3%, B3 19.3%, perianal 19.3%, prior CD-related surgery 61.3%	Median (IQR): 9 (3-21)	At second CTE/MRE: Anti-TNF alone: 20%, THIO alone 36%, MTX alone 5.3%, Anti-TNF + THIO 24%, Anti-TNF + MTX 5.3%, Budesonide 8%, Natalizumab 1.4%	Predictive role of radiologic response on long-term outcomes: CS use, hospitalization, and surgery	Serial CTE/MRE: first and follow-up (705 CTE/MREs): pre-therapy and after 6 mo or 2 CTE/MREs ⩾ 6 mo apart (during maintenance therapy)	Median 4.6 yr (IQR: 1.6-7)
Fernandes, 2017, Spain[13]	RS	214 adults, 49.5% F, median age (IQR) 36.8 (16–77) yr, L1 76.6%, L3 23.4%, L4 10.3%, B1 44.4%, B2 26.2%, B3 29.4%, perianal 29.9%, prior intestinal resection 40.7%	Median (IQR): 7.4 (0-40.8)	THIO 54.7%, MTX 0.5%, Anti-TNF 18.7%	Predictive roles of MH and TH for hospital admission, surgery and MD escalation (start an IMD or biologic, escalate anti-TNF or switch to a different biologic)	MRE and IC performed within a 6-mo interval (median: 2.3 mo)	Median (IQR): 3.5 (1-7.9) yr Evaluation after 12 mo
Ripollés, 2016, Spain[41]	PS multicenter	51 adults, active disease, 47% F, median age (IQR) 35 yr (27-46), L1 57%, L2 21.5%, L3 21.5%, B1 57%, B2 10%, B3 33%, perianal 27.5%, history of surgery 33%	Median (IQR): 5 (2-10.3)	Active MD: Anti -TNF (IFX or ADA) 100% (63% combined with IMD)	Predictive role of TH on clinical outcome, change in MD, surgery	Clinical and US / CEUS at baseline, 12 wk and 1 yr after treatment	Median (IQR): 16 mo (12.2-32)
Orlando, 2018, Italy[44]	PS	30 adults, 33.3% F, mean age (± SD) 38.8 (± 14.5) yr, L1 40%, L3 60%, B1 53.3%, B2 40%, B3 6.7%, prior intestinal resection 40%	Mean ± SD: 9.8 ± 7.7	Active MD: Anti-TNF (IFX 53.3%, ADA 46.7%) Concomitant MD: 5ASA 10%, CS 10%, THIO 16.7%	Predictive role of TH and intestinal fibrosis on clinical outcome (hospitalization and surgery)	US and UEI at baseline, 14 and 52 wk after therapy	Median (range): 20 mo (10-38)

Laterza, 2018, Italy[15]	PS	57 adults, mean age (± SD) 45.3 (± 17) yr, 42.2% F, L1 38.6%, L2 8.7%, L3 52.6%, B1 31.6%, B2 54.4%, B3 14%, perianal 7%, previous surgery 22.8%	Mean ± SD: 7.4 ± 1	No therapy 10.5%, CS 26.3%, Anti-TNF 10.5%, CS + IMD 15.8%, CS + anti-TNF 8.8%, IMD + anti-TNF 8.8%, CS + IMD + anti-TNF 19.2%	Predictive role of a single and/or combined (CR, MH and TH) remission on outcomes (surgery, hospitalizations, MD changes - introduction of IMD or anti-TNF, anti-TNF escalation, switch to another anti-TNF, need for CS and deaths)	Clinical, endoscopic and CTE at baseline	Up to 36 mo

5ASA: 5-Amino salicylates; AB: Antibiotics; ADA; Adalimumab; Anti-TNF agents: Anti-tumoral necrosis alpha agents; AZA: Azathioprine; B: Behavior according to Montreal or Paris classification, with B1 inflammatory, B2 stricturing, B3 perforating, B2B3 both stricturing and perforating; CD: Crohn's disease; CEUS: Contrast-enhanced ultrasound; CR: Clinical remission; CS: Corticosteroids; CTE: Computed tomography enterography; F: Female; IC: Ileocolonoscopy; IFX: Infliximab; IH: Intestinal healing; IMD: Immunomodulators; IQR: Interquartile range; L: Location according to Montreal or Paris classification, with L1 distal 1/3 ileum ± limited cecal disease, L2 colonic, L3 ileocolonic, L4 upper proximal disease with L4a upper disease proximal to the ligament of Treitz, L4b upper disease distal to the ligament of Treitz and proximal to distal 1/3 ileum; MD: Medication; MH: Mucosal healing; MRE: Magnetic resonance enterography; MTX: Methotrexate; N/A: Not available; PS: Prospective; RS: Retrospective; SD: Standard deviation; TH: Transmural healing; THIO: Thiopurines; UEI: Ultrasound elasticity imaging; US: Ultrasonography.

those with active inflammation[43].

Long-term stable medication: Eder *et al*[42] also included "no need of corticosteroids" in long-term CR, and found IH to be a good predictor for this outcome. A Spanish study showed the IH group to have significantly less therapy escalation and longer time until therapy escalation *vs* the group with only MH and *vs* the no healing group[13]. Deepak *et al*[14] showed that TH significantly decreased the risk of corticosteroid use by over 50%. Another Spanish study found that three quarters of patients who did not change medication had sonographic improvement or TH *vs* only 8% of patients who needed medication change or surgery[41]. Children with TH had a significantly lower percentage of requiring any switch in therapy *vs* those without TH[43].

CD-related hospitalization-free status: Eder *et al*[42] also included "no hospitalization" in long-term CR, and found IH to be a good predictor for this outcome. In another study, IH was shown to be significantly associated with lower hospitalization rate and longer time until hospital admission *vs* MH and *vs* NH[13]. Lastly, complete CTE/MRE remission decreased the risk of hospitalizations by over two-thirds[14].

CD-related surgery-free status: IH was associated with significantly lower surgery rates *vs* MH and *vs* NH, and significantly longer time to surgery *vs* the other groups, without any difference between MH and NH[13]. Deepak *et al*[14] found that only "complete response" decreased the risk of surgery by over two-thirds. In another study, significantly less surgery was found to be required in patients with a strain ratio of < 2 at baseline, showing that less intestinal fibrosis is predictive for a better course of CD[44]. Lastly, in pediatric patients, the rate of CD-related surgery was significantly lower in those with TH *vs* no TH[43].

Limitations of the included studies: In essence, four studies were retrospective[13,14,42,43], two had low number of patients[42,44], three did not include IC[41,43,44], and none of the studies used a validated score for CSI. In addition, only one CSI examination was performed in three studies[13,15,43], thus not allowing for a dynamic assessment of transmural changes. No study included the influence of TH on long-term sustained TH, disability, and BD. More details are presented in Table 3.

DISCUSSION

The influence of TH or IH on long-term outcomes represents a new concept, as was described in this review and evidenced by the fact that all the relevant studies have been published since 2016. Six of the seven studies demonstrated that patients with IH[13,42] or TH[14,41,43,44] had significantly higher rates of favorable long-term outcomes *vs* those with persistent inflammation, including long-term CR[41-43], fewer therapeutic changes[13,14,41-43], reduced rate of CD-hospitalization[13,14,42,44] and of CD-related surgery[13,14,41,43,44]. Also, IH (evaluated by CSI and IC) was superior to MH alone (at IC) in predicting significantly better long-term outcomes[13,42]. The poor agreement between MH and TH[13-15], showing that active inflammation beyond the mucosa could persist even in patients with MH, is in accordance with previous data[11,12,23,27]. Therefore, MH does not seem to be an adequate surrogate marker of IH. Since treating to a TH target leads to better patients' outcomes than those of patients without TH, TH should be incorporated in the

Table 2 Definitions used in the included studies

First author, year, country	CR definition; percentage	MH: definition; percentage, timing	Cross-sectional imaging method (details)	TH (± IH): definition	Percentage of TH, timing	Agreement MH-TH
Eder, 2016, Czech Republic[42]	CDAI < 150	MH: ⩾ 50% decrease in SES-CD; 62%, after induction	MRE (score: SEAS-CD)	TH: ⩾ 50% decrease in SEAS-CD IH: TH + MH: ⩾ 50% decrease in both SES-CD and SEAS-CD	TH: 38%, IH: 31%, both after induction	N/A
Sauer, 2016, United States[43]	According to PGA	No IC	MRE (no score; "all or none" approach - abnormal BWT, increased enhancement)	TH: lack of active inflammation, complete MRE healing (normal BWT and no increased enhancement)	TH: 35.6%, at inclusion	N/A
Deepak, 2016, United States[14]	N/A	Inactive IC; 17.3%, at 2nd CTE/MRE (data missing in 61% of patients)	MRE/CTE (score by[37]): BWT ⩾ 3 mm, mural hyperenhancement, or intramural hyperintense T2 signal; segments length; comb sign, peri-enteric inflammation (absent, localized edema, inflammatory mass, abscess), fistula, stricture	TH: reduction in lesion length to 0 cm and a score < 1 for all other parameters (decreased enhancement or length of disease, no worsening of parameters of active inflammation - dilated vasa recta/comb sign, perienteric inflammation (edema, phlegmon, or abscess), or fistula	Complete radiologic responders: 37%, at 2nd CTE/MRE	Of inactive ileum at IC: 46% with active disease at 2nd CTE/MRE
Fernandes, 2017, Spain[13]	N/A	Inactive IC: no mucosal ulceration; in operated patients - Rutgeerts score 0-1; Inactive IC: 39.4% MH group = inactive IC + active MRE: 24.3%	MRE (active: BWT > 3 mm, increased contrast enhancement, and complications - stricture, abscess, or fistulae; additionally: fat creeping and comb sign)	IH (TH) group: MH + inactive MRE NH: active endoscopy, irrespective of the MRE findings	Inactive MRE: 25.7% IH group: 15.4% NH group: 60.3%	Significant low correlation between inflammation assessed by MRE and IC (Spearman's rho = 0.244, P < 0.001)
Ripollés, 2016, Spain[41]	HBi < 5 and normal CRP, without CS	No IC	US/CEUS (sonographic score: transmural inflammation - BWT, color Doppler grade, mural enhancement; extramural involvement, and obstructive disease)	TH: BWT < 3 mm, besides color Doppler grade 0 and the absence of complications, regardless of the persistence of parietal enhancement	TH: 14%, at 12 weeks and 30%, at 52 wk	N/A
Orlando, 2018, Italy[44]	N/A	No IC	US/UEI (bowel wall stiffness: strain ratio between mesenteric tissue and bowel wall; strain ratio ⩾ 2 = severe ileal fibrosis	TH: BWT ⩽ 3 mm	TH at 14 and 52 wk: 27% and 30%, respectively. Baseline strain ratio: lower in those with TH (P < 0.05)	

Laterza, 2018, Italy[15]	HBi ⩽ 4; 56% at baseline	MH: SES-CD ⩽ 2; 19%, at baseline	CTE (qualitative judgment on transmural activity, based on lesions: BWT, stenosis, target sign, comb sign, lymphadenopathy, fistula, abscess, sinus tract, fibrofatty proliferation, perienteric stranding, free fluid in the abdomen)	TH: absence of typical CTE lesions	TH: 17.5%, at baseline	Agreement between CTE and IC in 47% (k = – 0.05; P = 0.694); Agreement between CTE, IC and HBi in 18% (k = 0.01; P = 0.41), TH: detected in 27% with MH

BWT: Bowel wall thickness; CD: Crohn's disease; CDAI: Crohn's disease activity index; CEUS: Contrast-enhanced ultrasonography; CR: Clinical remission; CRP: C-reactive protein; CTE: Computed tomography enterography; HBi: Harvey-Bradshaw index; IC: Ileocolonoscopy; IH: Intestinal healing; MH: Mucosal healing; MRE: Magnetic resonance enterography; N/A: Not available; NH: No healing; PCDAI: Pediatric-CD activity index; PGA: Physician global assessment; SEAS-CD: Simple enterographic activity score for CD; SES-CD: Simple endoscopic score in CD; TH: Transmural healing; UEI: Ultrasound elasticity imaging; US: Ultrasonography.

concept of DR.

As the above results showed, however, TH may be more difficult to reach than MH. It had been suggested that TH needs a longer period of therapy (*i.e.,* > 1 year). The sonographic response after 12 wk of anti–TNF therapy has also appeared to be more pronounced than in the maintenance period[41], and this result is similar to findings from a previous MRE study[23]. Therefore, TH could probably be achieved earlier but only if aggressive therapy is used and applied in a timely manner. It was also previously considered that, when significant BD was already present, the effect of therapy on transmural lesions might be less effective[12]. The collective population that comprised the seven studies in this review had a relatively long duration of disease already[13-15,41-44] and many patients had complicated behavior (stricturing and/or fistulizing) and previous surgery (BD)[13-15,41,44]. These facts could explain the relatively small percentage of patients reaching TH. Ripollés *et al*[41] demonstrated that initial stricture was the only sonographic feature predictive of negative response, while Deepak *et al*[14] found that penetrating behavior was a risk for hospitalization for active disease and showed a trend towards increased surgical risk. Laterza *et al*[15] provided evidence that TH following anti-TNF therapy was mostly achieved in the absence of significant bowel fibrosis.

CSI techniques are of paramount importance, not only in assessing TH but also for determining BD, while IC is not accurate enough. A recent study showed that surgical resections (26%) were not associated with the presence of severe lesions at IC, while stenosis or intra-abdominal fistulae (part of BD) at MRE correlated significantly with a higher risk of surgery[47]. Unfortunately, no study in this review was designed to include the CD Damage Score - the Lémann index (LI)[2,26] - at baseline or to predict the role of TH on further LI. In a prospective study by Fiorino *et al*[48], 39.4% of CD patients had BD at diagnosis. Even if treatment with anti-TNF agents was able to reverse BD in a subgroup of CD patients[49], within the first 10 year of the disease at least two thirds of the patients demonstrated significant BD[50]. These data provide support, once more, for the theory that earlier introduction of disease-modifying therapy might prevent the onset of irreversible BD[6,12].

A key strength of this narrative review is its being the first of its kind, to the best of the author's knowledge. It showed the significance of including TH as a new therapeutic goal and the importance of using CSI techniques in assessing TH. This review also has several limitations. First, since the concept of TH related to long-term outcomes is recent, the number of studies is small; however, all available full-text manuscripts in the literature were included, representing studies of pediatric and adult patients and, given the paucity of data, prospective and retrospective studies. Second, no manuscript addressed all long-term outcomes; although, three of the four mentioned outcomes were included in five studies[13,14,41-43]. Third, different CSI techniques, scores and parameters were used to define TH.

Do we know which method is the most accurate (gold standard) to assess TH? Reviews and meta-analyses[51,52] have highlighted the high accuracy (> 80%-90%) of CTE, MRE, and US for the diagnosis of CD, assessment of disease activity, or abdominal complications of CD, with no significant differences among these procedures in terms of sensitivity and specificity[22]. However, the use of CTE in children should be limited to exceptional circumstances (when US and/or MRE cannot be used)[53], as it could increase the risk of developing malignancies[54]. Castiglione *et al*[32] recently showed that TH rates achieved after anti-TNF therapy (detected by US and MRE) were approximately equal (25% *vs* 23%, k = 0.90; P < 0.01) in patients with ileocolonic CD. They concluded that these two techniques were similar in assessing TH, with the choice being largely determined by local availability, experience, cost and patient preference[55].

Nowadays, given their non-invasiveness, non-irradiation and high accuracy, MRE and US are considered the most appropriate techniques to monitor CD patients after treatment[18]. Benefits and limits of CTE, MRE and US

Table 3 Outcomes of patients achieving transmural healing and intestinal healing

First author, year, country	Long-term CR; percentage; other findings	Change in medication	Reduction in hospitalizations for active CD	Reduction in CD-related surgery	Other findings/ Comments	Limitations
Eder, 2016, Czech Republic[42]	38%; TH: not useful for predicting long-term CR IH: predicts long-term CR, $P = 0.02$ (75% Sen, 72% Spe)	N/A	N/A	N/A	MH: borderline significance ($P = 0.06$) in predicting long-term CR (50% Sen, 80% Spe)	RS, Low number of patients, Only ileocolonic CD, No MRE, No IC by the end of 1 yr therapy
Sauer, 2016, United States[43]	TH: 88.9% *vs* 44.6% of those with MRE active inflammation (no TH), $P < 0.001$	TH: 8.3% *vs* no TH: 44.6% (switching from IMD to biologic and changing type of biologic, $P < 0.001$)	N/A	TH: 2.8% *vs* No TH: 18.5%, $P = 0.024$	N/A	RS, All MRE - part of patient care, No standardized MRE score, No MRE, No IC at end of follow-up
Deepak, 2016, United States[14]	N/A	Complete or partial radiologic response decreases risk for CS use by over 50% [HR: 0.37 (95%CI: 0.21-0.64), $P < 0.001$ and 0.45 (95%CI: 0.26-0.79), $P = 0.005$ respectively]	Complete response decreases risk of hospitalizations by over two-thirds [HR: 0.28 (95%CI: 0.15-0.50), $P < 0.001$]; also partial response decreases risk [HR: 0.54; (95%CI: 0.32-0.92), $P = 0.04$]	Complete response decreases risk of surgery by over two-thirds [HR: 0.34 (95%CI: 0.18-0.63)], $P < 0.001$	First data to demonstrate the magnitude and significance of radiological response as a treatment target and endpoint; Penetrating behavior is a risk for hospitalization for active disease and shows a trend towards increased surgical risk	RS Tertiary referral center Not all IC available
Fernandes, 2017, Spain[13]	N/A	IH: less therapy escalation *vs* MH and *vs* NH (15.2% vs 36.5%, $P = 0.027$ and vs 54.3%, $P < 0.001$); IH: longer time until therapy escalation *vs* MH, $P = 0.046$ and *vs* NH, $P < 0.001$; MH better outcome than NH	IH: hospitalization rate lower *vs* MH and *vs* NH (3.0% *vs* 17.3%, $P = 0.044$ and *vs* 24.0%, $P = 0.003$); no difference MH *vs* NH IH: time until hospital admission longer *vs* MH, $P = 0.046$ and *vs* NH, $P = 0.008$	IH: surgery rates lower *vs* MH and *vs* NH (0% *vs* 11.5%, $P = 0.047$ and *vs* 11.6%, $P = 0.027$); no difference MH *vs* NH IH: longer time to surgery *vs* MH ($P = 0.045$) and *vs* NH ($P = 0.044$)	Endoscopic remission (OR: 0.331, 95%CI: 0.178-0.614, $P < 0.001$) and MRE remission (OR: 0.270, 95%CI: 0.130-0.564, $P < 0.001$): independently associated with a lower likelihood of reaching any of the studied outcomes	RS, dichotomous definition of IH and MH, No scores, No patients with stenosis, Interval between IC and MRE (up to 6 mo) Only baseline IC and MRE
Ripollés, 2016, Spain[41]	Good sonographic response at 52 wk predicts good long-term clinical outcome (2-3 yr) with a Sen of 78% and Spe of 81.3%; OR: 15.5	TH at 52 wk: 93% did not require change in medication/ surgery	N/A	TH/sonographic improvement at 52 wk: less likely to require change/ intensification in MD or surgery during follow-up *vs* no improvement (11% *vs* 65%, $P < 0.001$)	Changes in BWT: most important in assessment of the effects of therapy; 42% of patients without complications achieved TH *vs* only 5% with complicated behavior; Initial stricture: the only sonographic feature predictive for negative response ($P = 0.0001$)	No IC, No validated US-based activity score

Orlando, 2018, Italy[44]	N/A	N/A	Hospitalization rate decreases significantly with an increase in the number of parameters indicating remissions at baseline	Significant less surgery in patients with a strain ratio < 2 at baseline (P = 0.009)	No association between baseline BWT at US and therapeutic outcomes	Low number of patients, No IC, Single center study
Laterza, 2018, Italy[15]	N/A	Complete remission vs patients with one or two remissions (partial remission) *vs* no remission: differences among groups different only for the need of topical CS (P = 0.03)	Complete remission (CR, MH, TH): trend for fewer hospitalizations *vs* patients with only MH or TH or CR	N/A	Endoscopic remission: significantly less changes in therapy *vs* endoscopic activity (P = 0.02) Multiparametric (CR, MH, and TH) evaluation might have a better value to predict significant changes in therapy and hospitalization	Heterogeneous therapies CTE: qualitative non-validated score Only baseline clinical, IC and CTE evaluation

BWT: Bowel wall thickness; CD: Crohn's disease; CFREM: Clinical CS-free remission; CR: Clinical remission; CS: Corticosteroids; CTE: Computed tomography enterography; IC: Ileocolonoscopy; IH: Intestinal healing; IMD: Immunomodulators; MD: Medication; MH: Mucosal healing; MRE: Magnetic resonance enterography; N/A: Not available; NH: No healing; RS: Retrospective study; Sen: Sensitivity; Spe: Specificity; TH: Transmural healing.

have been extensively presented in recent reviews[53,55-61], systematic reviews and meta-analyses[52,62], and consensus guidelines[53,63-65]; therefore, they are beyond the scope of this review. Validated CSI scores to quantify activity in CD are mainly based on MRE[55,56,58]. A comparison between the three most used scores in adults with CD - Magnetic Resonance Index of Activity (MaRIA)[16,66], Clermont[67] and London[68] - was recently published[69]. All scores had high accuracy for evaluating CD activity, but MaRIA had better overall operational characteristics for its use in both clinical trials and clinical practice[69]. A recent paper questioned the role of MaRIA in properly assessing BD and as a prognostic factor. Fiorino *et al*[48] showed that BD and LI were independent prognostic factors for intestinal surgery [hazard ratio (HR): 3.21 and 1.11, respectively; P < 0.001] and for CD-related hospitalization during patient follow-up (HR: 1.88 and 1.08, respectively; P = 0.002 and < 0.001, respectively). Disease activity as expressed by the MaRIA score did not predict the disease course and the correlation between the LI and MaRIA score was weak (rho: +0.32; P < 0.001)[48]. Therefore, it appears that there are still some unanswered questions regarding the most appropriate score to use.

None of the studies included in this review used a validated index to quantify TH, even when a system score was used in three of the studies[14,41,42]. Some authors consider that in daily clinical practice, normalization of BWT (< 3 mm), without signs of hypervascularization, at MRE[23,25,30,32] and US[12,22,32,41,55], represent the best criteria for TH[18,32]. Only one study in this review used the above mentioned definition of TH, which was related to better outcomes[43]. However, Orlando *et al*[44] found no association between baseline BWT at US and therapeutic outcomes. Moreover, abnormal BWT detected at MRE (as a result of fibrosis and fibromuscular hyperplasia) may persist in the absence of a significant active inflammatory component[17], reflecting BD[70,71]. Some authors consider that extramural lesions should also be included in TH[40]. Even the STRIDE concept mentions that "resolution of findings of inflammation on CSI" should be achieved[8], but without clearly defining how that would be ideally quantified.

Considering all the presented data above, TH evaluated by CSI still remains an evolving concept[32] and its exact definition is not clearly established yet. Therefore, even if the studies included in this review had different definitions of TH (the third limitation listed above), they reflect the current literature. Moreover, the same criteria were used across each of the seven studies. Given all these remarks, the third limitation of this review is not as bad as it would appear.

A fourth limitation of this review is its inclusion of heterogeneous populations (adults and children) with different duration of CD, various phenotypes, and medications used.

CONCLUSION

Despite their heterogeneous design and methodological limitations, six of the seven identified studies demonstrated that achieving TH or IH was associated

with favorable long-term outcomes (≥ 52 wk), including sustained CR, less need of rescue therapy, less CD-related hospitalizations and less CD-related surgery. Since treating to a TH target leads to better patients' outcomes than those of patients without TH, TH should be incorporated in the concept of DR. Evaluation by CSI techniques appears crucial in monitoring response to therapy and assessing TH, with potential application in changing treatment paradigms, as well as our practice.

Since TH is achieved in only a minority of patients with MH, earlier and stronger therapeutic interventions should be employed to reach higher rates of TH. Further continuous tight monitoring in order to maintain TH may prevent BD and disability. As IH (TH plus MH) appeared superior to MH alone for long-term outcomes, IH may become the future therapeutic endpoint in the treat-to-target strategy and an indispensable parameter in decision algorithms, with the view of altering natural history of CD, not only in clinical trials but also in daily clinical practice.

PERSPECTIVES ON FUTURE RESEARCH

Several aspects remain to be clarified regarding the ideal definition of TH and the best scores/parameters to use. Further studies should standardize and validate these aspects. Prospective well-designed multicenter trials (including stratified populations or treatment-naïve patients, and using both CSI and IC) are required to definitively assess the benefits of TH/IH on long-term outcomes, including BD and disability. More research is also warranted to better define the role of TH/IH (and timing of their assessment) in the era of personalized treatments targeted to individual patients.

Whether highly accurate, non-irradiating, non-invasive CSI techniques are able to replace endoscopy in monitoring response to therapy and be used as surrogate to endoscopy for MH represent other challenging fields of research. Novel biomarkers assessing fibrosis by ultrasound elastography or advanced MRE techniques and their use in identifying potential patients for TH could represent another promising research field. The cost-effectiveness of this tight control algorithm guiding therapy to a TH target should also be investigated *vs* MH alone. Finally, the predictive role of long-term TH (after long periods of maintenance therapy) for discontinuing or de-escalating treatment represents yet another interesting topic.

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