Targeting Mucosal Healing in Crohn's Disease

Michael F. Picco, MD, PhD, and Francis A. Farraye, MD, MSc

Dr Picco is an associate professor of medicine, consultant, chair of the Division of Gastroenterology and Hepatology, and co-director of the Inflammatory Bowel Disease Center at Mayo Clinic in Jacksonville, Florida. Dr Farraye is a senior associate consultant in the Division of Gastroenterology and Hepatology and director of the Inflammatory Bowel Disease Center at Mayo Clinic.

Address correspondence to:
Dr Michael F. Picco
Mayo Clinic
Division of Gastroenterology and Hepatology
4500 San Pablo Road
Jacksonville, FL 32224
Tel: 904-953-6970
Fax: 904-953-6225
E-mail: picco.michael@mayo.edu

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Abstract: The goals of medical treatment for Crohn's disease are to induce remission and prevent long-term complications. The assessment of disease activity and response to therapy has moved beyond symptom-based measures to more objective ones, including mucosal healing. Studies of medical therapies target mucosal healing, or more accurately endoscopic remission, as an important treatment outcome. Mucosal healing leads to higher rates of sustained clinical remission and lower rates of hospitalization and disease-related surgery. Although an important goal, treating to the endpoint of mucosal healing has significant limitations. Studies validating mucosal healing are largely based on ileocolonoscopy, which is invasive and limits visualization to the colon and terminal ileum. Other tests, such as capsule endoscopy, noninvasive radiographic imaging, and serum and stool biomarkers, hold promise as alternatives, but more studies are needed. Although patients may demonstrate endoscopic response with optimization of the current medical therapies and the novel therapies under study, many patients do not attain mucosal healing. If there is clinical remission but incomplete mucosal healing after optimization of a therapy, it is not clear whether that therapy should be abandoned. However, despite these limitations, mucosal healing is an important treatment goal for the evaluation of new and existing therapies for Crohn's disease both in clinical studies and in practice.

Crohn's disease (CD) is an inflammatory bowel disease that, without effective therapy, typically progresses from a mucosal to a transmural disease in the majority of patients, resulting in penetrating or stricturing complications. This process can develop despite a disease course that may include periods of clinical remission.[1] In the prebiologic era, rates of complications and surgery were high. In a consecutive series of CD patients, 18% and 70% developed stricturing and penetrating (including perianal disease) complications, respectively, at 20 years.[2] Similarly, in a population-based study from Olmsted County, rates of developing complications were 34% and 51% at 5 and 20 years, respectively, when perianal disease was excluded.[3] Rates of surgery for CD approached 80%.[4]

In the last 20 years, biologic therapies in the form of antibodies to tumor necrosis factor (anti-TNF), interleukin (IL)-12 and -23, and integrins have revolutionized the treatment of CD.[5] Over this period, the assessment of CD activity and efficacy of therapy has moved beyond clinical symptoms to objective measures obtained through endoscopy, radiology, and serum and stool biomarkers. It has been argued that the ultimate goal of treatment has become mucosal healing (MH). In 2015, MH was endorsed by the International Organization for the Study of Inflammatory Bowel Disease as an important treatment goal associated with better long-term outcomes.[6] MH, or more accurately endoscopic remission, is most commonly defined as the absence of mucosal ulceration in the area within reach of the colonoscope.[7] This article presents the current evidence for the importance of MH as a primary treatment goal for CD, the ability of existing medications to achieve this goal, and the limitations of adoption of MH into clinical practice.

Outcomes of Mucosal Healing

Clinical disease assessments such as the Crohn's Disease Activity Index (CDAI) and the Harvey-Bradshaw Index are poor subjective measures of CD activity and response to therapy.[8] Ileocolonoscopy provides information essential to the management of the majority of CD patients because approximately 70% will have disease of the ileum, colon, or both.[4] Early evidence showed that among patients with colonic CD, deep colon ulcerations at ileocolonoscopy predicted the likelihood of colectomy. At follow-up of 1, 3, and 8 years, rates of colectomy were 31%, 42%, and 62% for patients with this finding compared to 6%, 8%, and 18%, respectively, for patients without it.[9]

Evidence from incident cases of inflammatory bowel disease in Norway from 1990 to 1994 suggested that MH was associated with a better prognosis.[10] Ulcerative colitis (UC) patients with MH at 1 year after diagnosis had a lower rate of colectomy at 5 years. For CD, there was a trend toward lower surgical rates, but this did not reach statistical significance, perhaps related to the mixed population of colonic and ileal disease with different surgical risks and fewer patients with ileal disease at 1-year follow-up.

The benefit of MH attained after medical therapy for CD was demonstrated in a meta-analysis of 673 patients from 12 studies, which included 8 nonrandomized, prospective, observational cohort studies; 3 post-hoc analyses of randomized clinical trials; and 1 randomized clinical trial.[11] Of the included studies, 7 were with biologics (infliximab [Remicade, Janssen] and adalimumab [Humira, AbbVie]) and 5 were with other treatments, including immunomodulators. Patients had endoscopic assessment within 6 months of starting treatment and clinical or endoscopic follow-up for at least 50 weeks. Overall, 69% of patients with MH at first assessment maintained long-term clinical remission (at least 50 weeks) compared to 43% without MH. Among patients who had endoscopic assessment after 50 weeks, 94% with MH at initial assessment maintained long-term MH compared to 18% who initially had endoscopically active disease. There was also a trend to lower rates of surgery that did not reach statistical significance. In another meta-analysis that included retrospective studies, in addition to being associated with maintenance of clinical remission and fewer hospitalizations, MH had a significant protective effect for avoiding surgery.[12] For complete MH, the relative risk of surgery was 0.39, or 61% less, compared to when MH was not achieved.

The majority of patients who undergo surgery for active CD will have endoscopic recurrence that precedes clinical recurrence.[13] After ileocolonic resection, 70% of CD patients developed new endoscopic evidence for recurrence with pre-anastomotic ulcerations at 3 months. This is asymptomatic in one-third of patients but leads to clinical disease recurrence at 3 years in 86%.[14] Endoscopic appearance predicted the likelihood of clinical recurrence, as defined by the Rutgeerts score, which is based on the presence and number of erosions or ulcers at the pre-anastomotic neoterminal ileum.[15,16] For patients with MH at assessment, 80% maintained MH at 3 years. Furthermore, early intervention with infliximab after ileocolonic resection significantly improved endoscopic appearance at 1 year, with 82% having no recurrence compared to 8% treated with placebo.[17] This finding persisted at follow-up with a longer time to first endoscopic recurrence (3.4 vs 1.3 years) and to next surgery (4.9 vs 2.9 years) among patients originally assigned to the infliximab group.[18]

Alternatives to Ileocolonoscopy for the Assessment of Mucosal Healing

A significant limitation of MH is the reliance on ileocolonoscopy, which is invasive, costly, and limited to the evaluation of the terminal ileum and the colon. The Crohn's Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score for Crohn's Disease (SES-CD) are validated measures of endoscopic disease activity that allow for objective assessment of response to therapy.[19-21] While MH is important, in its absence endoscopic improvement is an easier target to attain as a treatment response, although its long-term effect on disease prognosis is not known. Endoscopic response can vary significantly compared to MH. This is illustrated in

post-hoc analyses of the MUSIC (Endoscopic Mucosal Improvement in Patients With Active Crohn's Disease Treated With Certolizumab Pegol) trial and the SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease) trial, which established the efficacy of certolizumab pegol (Cimzia, UCB) and infliximab, respectively, in CD. In the MUSIC trial, where MH was defined as a CDEIS of less than 3, only 4% had MH at week 10.[22] This is compared to more than 50% who achieved endoscopic response and more than 35% with endoscopic remission (minimal erosion/ulceration). In the SONIC trial, endoscopic response, defined as at least a 50% improvement in CDEIS from baseline endoscopy, was attained in 65% of patients at week 26 compared to 48% with MH.[23,24]

The timing of assessment of MH following treatment initiation is also variable, and the optimal time for evaluation has not been validated. However, based on literature review and expert opinion, a repeat colonoscopy 6 to 9 months following the start of therapy has been recommended.[6] This should allow for sufficient time to assess for a treatment effect and provide a standard approach for clinicians. More data are needed to address this issue.

The reliance on clinical noninvasive symptom-based indices to enroll CD patients in many clinical studies followed by ileocolonoscopy for assessment of treatment response limits the validity of the conclusions regarding MH. In the SONIC study, which compared combination therapy with azathioprine and infliximab to infliximab alone or azathioprine alone for active CD based on CDAI, 34%, 32%, and 41% of enrolled patients, respectively, had no evidence of mucosal inflammation at ileocolonoscopy.[23] This emphasizes the need for objective assessment of disease activity prior to treatment initiation.

Radiographic Imaging

Noninvasive assessments of MH, which include radiographic imaging, capsule endoscopy (CE), and serum and stool biomarkers, represent potentially more attractive alternatives to ileocolonoscopy. Because MH is limited to the assessment of the mucosal surface, it does not take into account coexistent bowel wall thickening or stricturing or penetrating complications. Computed tomography enterography (CTE) provides an essential evaluation for transmural complications and extraintestinal findings.[25] Among patients with small bowel CD, 64% with active CD in the terminal ileum by CTE had endoscopically normal findings.[26] Magnetic resonance enterography (MRE) is comparable to CTE as an alternative to ileocolonoscopy. CTE and MRE have equal sensitivity (80%) and similar specificity (88% and 82%, respectively) for detecting active mucosal inflammation of the terminal ileum.[27] However, this research was largely based on ileocolonoscopy as the reference standard, so the role of enterography for patients with disease confined to the more proximal small bowel is not clear.

The use of CTE and MRE as an alternative to ileocolonoscopy in the treatment of active CD is also unclear. In a prospective study, CTE was shown to alter management plans in half of patients with either suspected or established CD, but this was not compared to ileocolonoscopy, and patient outcomes were not reported.[28] In a retrospective study, CD patients with small bowel disease who were treated with immunomodulators or biologic therapies underwent CTE or MRE at baseline and at follow-up after 6 months of therapy.[29] Therapeutic response, defined as improvement in imaging, was observed in 37%. MH was not measured.

There is, however, limited evidence for the use of MRE to guide therapy where ileocolonoscopy is used as a reference standard. In a small prospective study, CD patients treated with corticosteroids or adalimumab underwent MRE and ileocolonoscopy at baseline and after 12 weeks of therapy.[30] The rate of MH, defined as the absence of ulcers in all segments by MRE, was 50% using the Magnetic Resonance Index of Activity (MaRIA) score, with good correlation (kappa=0.71), sensitivity of 75%, and specificity of 80% compared to ileocolonoscopy. In addition to assessment for ulcers, the MaRIA score includes the presence of wall thickness, relative contrast enhancement, and edema.[31] Ulcer healing led to decreased wall thickening and edema. Although encouraging, conclusions from this study need confirmation, as they are based on interpretation by expert MRE radiologists and limited by small patient numbers.

Capsule Endoscopy

CE, in conjunction with CTE and MRE, is an option for some patients with proximal small bowel CD. Validated measures of CD activity on CE include the Lewis score[32,33] and the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI).[34] In a meta-analysis of 5 observational studies, MH after treatment was associated with endoscopic improvement at 3 to 24 months of follow-up according to the CECDAI or Lewis score.[35] Among patients in clinical remission, MH was found in only 15%.[36] In fact, of patients in clinical remission, 21% had moderate to severe inflammation on CE, emphasizing the discordance of clinical symptoms with CE findings. However, these conclusions are based on observational studies that have small numbers of patients, only a minority of whom have disease proximal to the terminal ileum, and are limited to patients without significant small bowel narrowing that could lead to capsule retention. MRE in this selected population correlated poorly with CE findings.

Biomarkers

Serum and stool biomarkers are potential noninvasive ways to assess MH in CD. In a meta-analysis of symptomatic patients, fecal calprotectin was superior to C-reactive protein (CRP) as a surrogate marker for determining endoscopic disease activity for both UC and CD.[37] For CD, CRP measurement performed poorly, with a sensitivity of 0.49 and a specificity of 0.92. Fecal calprotectin had better specificity for UC compared to CD (0.79 vs 0.67, respectively), but had the same sensitivity (0.87 for both). The cutoff for endoscopic activity was 50 μg/g of stool. In a separate meta-analysis that had a much higher cutoff for disease activity (250 μg/g) and included patients in symptomatic remission, as expected, specificity increased to 0.81 but sensitivity remained high at 0.80.[38] Fecal calprotectin is a less sensitive measure of MH for ileal CD compared to ileocolonic CD.[39]

Among patients with active CD by ileocolonoscopy, the use of serum and stool biomarkers combined with CDAI to guide therapy was more successful at attaining MH than CDAI alone. In the CALM (Effect of Tight Control Management on Crohn's Disease) study, biologic-naive patients with active CD at ileocolonoscopy were randomized, after a course of prednisone, to a tight control group and a clinical management group for disease monitoring.[40] In the tight control group, active disease was defined by fecal calprotectin of at least 250 μg/g, CRP of at least 5 mg/L, CDAI of at least 150, or prednisone use in the week prior to assessment. The clinical management group was defined by a CDAI decrease of less than 100 compared with baseline, CDAI of more than 200, or prednisone use. Adalimumab therapy was initiated for active disease, and patients were assessed at weeks 12, 24, and 36. If disease activity was present, treatment was escalated to weekly therapy. MH was found in 46% of the tight control group compared to 30% of the clinical management group. Although this study was limited by an open-label design, it represents a real-world approach of the use of clinical symptoms and biomarkers to guide treatment leading to higher rates of MH.

However, while fecal calprotectin shows some promise as a surrogate marker for MH, differences in study design, measurement, threshold cutoff for MH, and patient selection can limit its usefulness in clinical practice. A reasonable approach, as recommended by a review, would be to check fecal calprotectin in a patient at diagnosis with active disease at endoscopy and when endoscopic remission has been achieved.[41] This would allow for establishing a level of this biomarker for remission and disease activity that correlates with endoscopic findings. However, the recommended use of defined cutoffs for endoscopic activity is problematic, with the range between active disease and MH in an individual patient providing the best information to guide care in practice.

Mucosal Healing and Crohn's Disease Treatments

Corticosteroids

Although corticosteroids remain an accepted therapy for the induction of remission in active CD, clinical improvement does not correlate with endoscopic findings. Only a minority of patients demonstrate MH either with initial treatment or at follow-up. Patients in clinical remission maintained on prednisolone fared no better than those who had the medication tapered off.[42,43] MH after treatment of active CD with oral enteric release budesonide was found in only 24% of patients at 1 year despite the exclusion of 19% of patients who flared or were intolerant to the medication.[44] Budesonide also offered no benefit at preventing endoscopic recurrence after surgery for ileal or ileocolonic CD compared to placebo.[45] These studies further support practice guidelines recommending that corticosteroids have a limited role in the treatment of active CD.[5]

Immunomodulators

Although the immunomodulators azathioprine and methotrexate have been more recently relegated to a secondary role by some experts in the treatment of CD, as monotherapy or combination therapy they may lead to MH in some patients (Table 1). In 2 observational studies of azathioprine after corticosteroid withdrawal, MH occurred in 70% and 40% of patients, respectively.[46,47] These disparate findings are likely due to differences in patient selection, lack of information regarding pretreatment endoscopic assessment, awareness of treatment assignment, and method of MH assessment (ileocolonoscopy vs radiographic imaging). Furthermore, the duration of therapy may also have been a factor, with higher rates of MH at 18 months compared to 6 months.

Stronger evidence comes from a randomized trial of corticosteroid-dependent patients with Crohn's ileocolitis or colitis treated with oral budesonide or azathioprine followed by prednisolone tapering.[45] All patients had ileocolonoscopy within 14 days of enrollment and at 1 year with CDEIS reported. MH was attained in 73% of the azathioprine group at 1 year compared with 24% of the budesonide group. However, 21% withdrew before 1 year due to flares or medication intolerance.

There is also some evidence for MH with azathioprine in children with CD. In an observational study, 29 pediatric patients with ileocolonic CD naive to azathioprine or other immunomodulators were given azathioprine to maintain remission after induction therapy with enteral

Table 1. Mucosal Healing With Azathioprine and Methotrexate

Study	Study Design/ Disease Activity	Disease Location	Concomitant Medication	Length of Follow-Up	Mucosal Healing	Comments
Azathioprine						
Mantzaris et al[45] N=37	RCT/ remission	IC: 63% C: 37%	CS taper	1 year	73%	8 patients WD
D'Haens et al[46] N=20	PNRC/ remission	IC: 65% C: 35%	None	24 months	70%	Endoscopy 19 months after CS stopped
D'Haens et al[47] N=19	RNRC/ active	I: 100%	CS taper	18 months	40%	Active CD after ileocecal resection 4 patients WD
Giugliano et al[48] N=29	PNRC/ active	IC: 52% I: 24% C: 24%	Enteral nutrition or CS taper	1 year	48%	8 patients WD
Colombel et al[23] (SONIC) N=170	RCT/ active	IC: 41% I: 40% C: 19%	CS taper	26 weeks	17%	ITT
D'Haens et al[49] N=81	RCT/ remission (postoperative)	IC: 100%	Metronidazole for 3 months	1 year	45%	ITT
Methotrexate						
Laharie et al[50] N=18	PNRC/ remission	IC: 56% C: 39% I: 5%	None	24 months	11%	None
Huang et al[51] N=35	RNRC/ active	I: 24%	CS dependent or refractory	36 weeks	47%	18 patients WD

C, colon only; CD, Crohn's disease; CS, corticosteroid; I, ileum only; IC, ileocolonic; ITT, intention-to-treat analysis; PNRC, prospective nonrandomized cohort; RCT, randomized clinical trial; RNRC, retrospective nonrandomized cohort; SONIC, Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease; WD, withdrew prior to assessment for mucosal healing.

nutrition or corticosteroids. Patients in remission at 1 year underwent ileocolonoscopy.[48] MH was attained in 48%, but 8 patients dropped out before 1 year.

There may be a role for azathioprine in the maintenance of MH in CD patients after surgery. In the most convincing study, after ileocolonic resection, patients were randomized to metronidazole for 3 months and either azathioprine or placebo for 12 months.[49] The likelihood of significant endoscopic recurrence, as measured by the Rutgeerts score, was 44% in the azathioprine group compared to 69% in the placebo group.

The SONIC study has challenged these reports of azathioprine's efficacy for MH. In this study, among patients receiving azathioprine monotherapy, 36% withdrew before week 26.[23] Among the remaining patients, MH was found in only 17%. Due to its rigorous study design, this trial presents the most reliable information on the rate of MH for azathioprine monotherapy. Although this low rate may have been in part due to a shorter follow-up, the finding casts doubt on the previously reported higher rates of MH with azathioprine. This study showed that the best role for azathioprine was in combination with infliximab, with 44% attaining MH compared to 30% with infliximab alone.

In summary, while MH with azathioprine monotherapy may be attainable in some patients with active CD, methodologic differences may be responsible for variability in MH. This variability is most likely due to differences in study design, including observational vs randomized trials, time of assessment of MH, and high rates of patient withdrawal.

Evidence for MH with methotrexate treatment in CD is based on parenteral (subcutaneous or intramuscular) administration (Table 1). In a consecutive series of patients who were in clinical remission for 3 months off corticosteroids, MH was attained in 11% of the methotrexate group after a mean follow-up of 24 months vs 50% and 60% of the azathioprine and infliximab groups, respectively.[50] In a similar patient population, after a follow-up of 36 weeks, the rate of MH was 47% in the

methotrexate group and was the same in the thiopurine group.[51] This finding suggested that MH may take more time with methotrexate, but the conclusions are limited due to the observational study design and inclusion criteria. Furthermore, the majority of patients in the methotrexate group were refractory or intolerant to thiopurines, which may have led to lower rates of MH. Overall, the evidence for methotrexate achieving MH in CD is limited and based on small observational studies. There was significant variability due to study designs with different lengths of follow-up and inclusion of patients intolerant or refractory to thiopurines (Table 1).

Anti–Tumor Necrosis Factor Therapies

Anti-TNF agents were the first biologic therapies shown to be effective for the treatment of CD. Anti-TNF clinical trials have demonstrated not just clinical response and remission but also MH (Table 2). The strongest evidence for MH was demonstrated in the ACCENT (Maintenance Infliximab for Crohn's Disease) and SONIC studies of infliximab. In the ACCENT trial, patients with active CD were randomized after standard 3-dose induction therapy to every-8-week infusions or episodic treatment. For standard treatment, MH was 31% at 10 weeks and increased with every-8-week infusions to 50% at 1 year. This was compared to 0% after 1 treatment at week 10 and 7% for episodic treatment at 1 year.[52,53] In the SONIC trial, patients with active CD who were naive to anti-TNF therapy were randomized to azathioprine, infliximab, or a combination of these agents.[23] Clinical remission was highest with combination therapy (57%) compared with infliximab (44%) or azathioprine (30%) alone at 26 weeks. MH paralleled these findings with rates of 30% for infliximab alone and 44% for patients receiving combination therapy. Two post-hoc analyses of the SONIC trial clarified the role of infliximab levels and azathioprine in MH. The first showed that infliximab serum levels of 3.0 μg/mL or higher were associated with combination therapy and MH.[54] The second suggested that the added benefit of azathioprine on MH was only through improving therapeutic levels of infliximab and not by a direct synergistic effect, but more data are needed.[55]

For adalimumab, the strongest evidence comes from the EXTEND (Adalimumab Induces and Maintains Mucosal Healing in Patients With Crohn's Disease) trial, which randomized patients with moderate to severe ileocolonic CD after standard induction therapy to maintenance therapy and placebo for 52 weeks.[56] At week 12, 27% of patients on adalimumab maintenance had MH vs 13% with placebo. At week 52, the rates were 24% and 0%, respectively.

Data on MH with certolizumab pegol are limited. The MUSIC study was an open-label study that evaluated endoscopic response at weeks 10 and 54 following standard induction therapy with certolizumab pegol.[22] Therapy was continued at 400 mg every 4 weeks or escalated to every 2 weeks at week 10 if neither clinical response nor endoscopic remission was achieved or after week 10 for loss of clinical response.[57] At weeks 10 and 54, half of the patients had endoscopic improvement, but complete endoscopic remission or MH was seen in only 4% and 8%, respectively. Higher plasma levels of certolizumab pegol were associated with a higher likelihood of endoscopic remission.[22] Rates of MH are lower for certolizumab pegol compared to infliximab and adalimumab, although direct comparisons of certolizumab pegol are difficult due to differences in study design and in the patients enrolled.

Overall evidence for MH with anti-TNF agents for CD comes from 2 meta-analyses. Cholapranee and colleagues included 4 randomized trials in which pooled MH rates for induction therapy were 29% for anti-TNF agents vs 7% for placebo and, for maintenance therapy, were 28% and 1%, respectively.[58] There was a trend toward combination therapy with azathioprine being more effective. Shah and colleagues analyzed 12 studies, of which 7 included infliximab and/or adalimumab (3 nonrandomized studies, 3 post-hoc analyses of randomized trials, and 1 randomized trial).[11] Patients were followed after initial pretreatment ileocolonoscopy. Among patients with MH at initial assessment, 69% maintained long-term clinical remission compared to 43% without MH. Although there was a trend toward less CD-related surgery for patients with MH, this did not reach statistical significance. However, 93% of patients who had MH at initial assessment maintained long-term MH compared to only 18% who did not.

The evidence supporting MH is strongest for anti-TNF agents compared to other therapies in CD. It is supported by individual randomized trials and meta-analyses. MH rates for infliximab and adalimumab were comparable at approximately 30% depending on the timing of post-treatment assessment.[56,58] For infliximab, combination with azathioprine increased this rate to 44%.[23] MH rates were lower for certolizumab pegol at 8%, but this is based on fewer studies with this agent.[57]

Antibodies to Integrins

Antibodies to integrins are effective in the treatment of CD. The first of these agents, natalizumab (Tysabri, Biogen), demonstrated efficacy in a randomized clinical trial compared to placebo, but MH was not measured.[59,60] In a retrospective cohort, after a mean duration of 14 months of natalizumab treatment, 42% of patients demonstrated MH.[61] Vedolizumab (Entyvio, Takeda) is a safer alternative. It is effective for induction and maintenance therapy

Table 2. Mucosal Healing With Biologic Therapies

Study	Study Design/ Disease Activity	Disease Location	Concomitant Medication(s)	Length of Follow-Up	Mucosal Healing	Comments
TNF Inhibitors						
Infliximab						
Colombel et al[23] (SONIC) N=338	RCT/active	IC: 41% I: 35% C: 24%	CS with taper	26 weeks	44% with azathioprine/infliximab 30% with infliximab	ITT
Regueiro et al[17] N=12	PNRC/ remission (postoperative)	IC: 100%	Imm: 36%	1 year	91% (9% recurrence)	None
Rutgeerts et al[53] (ACCENT) Endoscopy substudy N=46	RCT/ active	IC: 60% C: 28% I: 12%	CS with taper	10 weeks 54 weeks	31% 50%	12 patients WD by week 54
Adalimumab						
Rutgeerts et al[56] (EXTEND) N=129	RCT/active	I/IC/C: 90%	CS: 39% Imm: 39%	12 weeks 52 weeks	27% 24%	ITT
Certolizumab Pegol						
Hébuterne et al[57] N=89	PNRC/active	IC: 100%	Imm: 51% CS: 42%	10 weeks 54 weeks	4% 8%	ITT
Antibodies to Integrins						
Natalizumab						
Sakuraba et al[61] N=32	RNRC/active	IC: 81% C: 16% I: 3%	CS: 56%	14 months	42%	None
Vedolizumab						
Dulai et al[63] N=212	RNRC/active	IC: 63% C: 24% I: 14%	CS: 45.2% Imm: 23%	6 months 12 months	20% 63%	79 patients WD 168 patients WD
Anti–IL-12/-23 Therapy						
Ustekinumab						
Wils et al[65] N=47	RNRC/active	IC: 75% C: 13% I: 11%	Imm: 21% CS: 15%	27 months	39%	19 patients WD
Ma et al[66] N=141	RNRC/active	IC: 50% I: 29% C: 21%	Imm: 44% CS: 43%	46 weeks	27%: Endo 31%: Rad	Mucosal healing assessment 92 patients Endo 49 patients Rad

ACCENT, Maintenance Infliximab for Crohn's Disease; C, colon only; CS, corticosteroid; Endo, mucosal healing assessment by endoscopy; EXTEND, Adalimumab Induces and Maintains Mucosal Healing in Patients With Crohn's Disease; I, ileum only; IC, ileocolonic; IL, interleukin; Imm, immunomodulatory; ITT, intention-to-treat analysis; PNRC, prospective nonrandomized cohort; Rad, mucosal healing assessment by radiographic imaging; RCT, randomized clinical trial; RNRC, retrospective nonrandomized cohort; SONIC, Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease; TNF, tumor necrosis factor; WD, withdrew prior to assessment for mucosal healing.

for CD based on the results of GEMINI 2 (Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease), a randomized trial.[62] However, not all patients had an endoscopic assessment prior to enrollment in this trial, which used the outcome of clinical remission. Endoscopic response was not an endpoint of the trial.

MH was demonstrated in a retrospective cohort of 212 patients treated with vedolizumab with a median follow-up of 39 weeks.[63] Of these, 121 patients had follow-up endoscopy with rates of MH of 20% and 63% at 6 and 12 months, respectively, with a median time for MH of 33 weeks. Patients who had more severe disease at study entry or previous exposure to anti-TNF therapy were less likely to achieve MH. The conclusions of this study were limited by its retrospective study design, endoscopic follow-up in only 60%, and variability in follow-up intervals and the timing of assessment for MH (Table 2).

Overall, data on MH for antibodies to integrins are limited in CD. Natalizumab demonstrated a MH rate of 42%, but this agent is seldom used due to the potential for adverse effects.[61] The rate for vedolizumab was higher (up to 63%), but this conclusion is limited by retrospective study design and patient inclusion criteria.[63]

Anti–Interleukin-12/-23 Therapy

Ustekinumab (Stelara, Janssen), a monoclonal antibody that inhibits IL-12 and -23, is effective for moderate to severe CD. However, this conclusion is based on a study in which ileocolonoscopy was not required for enrollment and endoscopic remission/response was not measured.[64] Evidence for MH comes from 2 studies that were retrospective, limiting their conclusions (Table 2). The GETAID group reported 122 patients with response or remission. Of these, 47 patients underwent ileocolonoscopy, with 39% demonstrating MH.[65] Similarly, among 141 patients treated with ustekinumab followed for a median of 46 weeks, 92 had endoscopic visualization with MH achieved in 27% of these patients.[66] Nearly all had previous treatment with a biologic agent, suggesting that this was a more refractory population that would be less likely to achieve MH.

Unanswered Questions and Future Directions

MH is an attractive outcome for clinical studies, but most patients do not achieve this goal. This may be, in part, due to differences in CD severity and behavior. In addition, the majority of clinical studies failed to allow for dose optimization, which is currently part of clinical practice and might lead to higher rates of MH. Many patients demonstrate endoscopic response to a specific therapy, but the impact of this on prognosis is not clear. For such patients, if optimizing an existing therapy with dosing adjustments does not lead to MH, should that therapy be deemed a failure? This remains a dilemma for clinicians. More studies are needed that use validated endoscopic indices such as the CDEIS and SES-CD to understand the risks and benefits of the use of defined endoscopic response when MH cannot be attained with a particular therapy. Such studies with both existing and new therapies that allow for medication optimization are clearly needed and would have a large impact on clinical practice. Abandoning therapy when there is endoscopic response but not MH leaves patients with fewer options for treatment.

There are many unanswered questions about the role of MH for the management of CD. CD is a transmural disease, and the role of MH in preventing or reducing the risk of penetrating or fibrostenotic complications is important but takes years of follow-up to determine. How does the presence or absence of transmural complications or perianal disease impact the goal of MH? Can MH alter the natural history of CD for these patients? Finally, is MH the best long-term treatment goal for CD?

Conclusion

Objective testing of CD activity has replaced symptom-based assessments. Despite its limitations, MH has emerged as an important treatment goal associated with better long-term outcomes. MH can be assessed in the majority of patients by ileocolonoscopy. However, noninvasive methods, although used clinically, have not yet shown to be reliable for the assessment of MH, especially for small bowel CD, and more studies are needed. Although targeting MH may be the most important goal in the evaluation of therapeutic options in CD, it may not be attainable in clinical practice for many patients. For the clinician, practical questions regarding options and prognosis in patients with objective response to therapy but not MH have yet to be answered. Given its global acceptance as a treatment goal, future studies of CD therapies should focus more on MH as well as on histologic healing as an outcome, and should provide answers for patients and clinicians alike.

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