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REVIEW ARTICLE

Mucosal healing in inflammatory bowel disease: Expanding horizon

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Abstract
Management of inflammatory bowel diseases has witnessed paradigm shift from 5-aminosalicylic acid and glucocorticoids to various immunosuppressant and biological agents. Targets of therapy have also been changed drastically from symptomatic improvement to mucosal, histological healing, and recently transmural healing. Mucosal healing is associated with reduced need of steroid therapy, hospitalization, and surgery. However, whether mucosal healing alters the natural history of disease remains to be proven. Though assessment of mucosal healing is traditionally done by endoscopic examination, newer tests like fecal calprotectin, capsule endoscopy, and magnetic resonance enterography have also shown promising results. Various immunosuppressants and biologicals are the main therapy being used to achieve mucosal healing. This review focuses on the need for achieving mucosal healing, its long-term benefits, various methods and algorithm for diagnosis, and achievement of mucosal healing.

Keywords Inflammatory bowel disease · Mucosal healing · Histological healing · Target to treat approach

Introduction

Inflammatory bowel diseases (IBDs) include ulcerative colitis (UC) and Crohn's disease (CD), which are characterized by recurrent episodes of intestinal inflammation and mucosal ulcerations. UC involves mucosa predominantly; however, CD is associated with transmural granulomatous inflammation. As IBD is associated with relapsing and remitting course, preventing relapse of disease after achieving remission is one of the most important facets in its management. Traditionally, treatment of IBD has primarily focused on symptomatic relief. However, clinical remission poorly correlates with endoscopic improvement. In a recent study, out of 152 patients with IBD in clinical remission, 33% had both endoscopic and histological inflammation and 33% had active histological inflammation [1]. Such ongoing mucosal or histological inflammation is associated with increased risk of disease relapse and long-term disease-related morbidity and complications. So, achievement of disease remission beyond symptomatic relief is important for improvement in long-term disease-related morbidity.

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In this review, we have discussed definition of mucosal healing, its long-term benefits, various methods to diagnose it, drugs found to be useful to achieve mucosal healing, and finally, the newer concepts of histological and transmural healing.

Definition of mucosal healing

International Organization of IBD (IOIBD) has put forward definition of mucosal healing in CD as absence of all visible ulcers in all the visualized segments of gut mucosa [2]. Similarly, for UC, same task force put forward definition of mucosal healing as absence of friability, erosions, and ulcers in all examined segments of gut mucosa [3]. Various endoscopic scores have been used to document endoscopic activity and endoscopic remission (mucosal healing) in both UC and CD (Tables 1 and 2). In CD, Crohn's Disease Endoscopic Index of Severity (CDEIS), Simple Endoscopic Score for Crohn's Disease (SES-CD), and Rutgeert's score are the most frequently used endoscopy scores [4] (Tables 1 and 2). Mayo score and Ulcerative Colitis Endoscopic Index of Severity (UCEIS) score are partially validated and most commonly used endoscopic scores in UC [5]. As UC is only a mucosal disease, absence of friability, erosions and ulcers, appears to be a valid definition. However, due to transmural disease behavior in CD, mocosal ulcers alone appears to be an inadequate measure to judge

Table 1 Various endoscopic indices used in inflammatory bowel disease

Index	Variables
Indices used in Crohn's disease	
Crohn's Disease Endoscopic Index of Severity (CDEIS)	Deep and superficial ulceration, surface involved by disease, surface involved by ulceration in part of colon
Simplified Endoscopic Score-Crohn's Disease (SES-CD)	Size of ulcer, ulcerated surface, affected surface, and presence of narrowing
Rutgeert's score (for postoperative assessment)	Presence and extent of aphthous ulcers and normal or inflamed intervening mucosa
Indices used in ulcerative colitis	
Truelove and Witt's score	Mucosal assessment (granularity, hyperemia)
Baron score	Bleeding, vascular pattern
Modified Baron score	Vascular pattern, friability, ulceration, and bleeding
Sutherland score	Bleeding, friability
Mayo endoscopic subscore	Vascular pattern, erythema, friability, erosions and ulcerations, bleeding
Rachmilewitz score	Granulation, mucosal damage, vascular pattern, bleeding
Ulcerative Colitis Endoscopic Index of Severity (UCEIS)	Vascular pattern, bleeding, erosions/ulcerations

improvement or deterioration of the disease [6]. Deep remission is defined as clinical remission with mucosal healing [7]. Clinical remission in CD is defined as Crohn's Disease Activity Index (CDAI) ≤ 150 and in UC as Mayo rectal bleeding and stool frequency score of 0 with endoscopic score of ≤ 1 [7, 8]. Recently, the term "complete remission" has been coined especially in UC as histological healing in addition to endoscopic mucosal healing and clinical remission [9]. Detailed description of histological healing has been provided at the end of this review article.

Benefits of mucosal healing

Clinical course

In CD patients, mucosal healing increases chances of steroid-free clinical remission and decreases the rate of relapses. In a Norwegian population-based cohort study, mucosal healing in CD was associated with significantly less endoscopic inflammation after 5 years ($p = 0.02$), decreased requirement of steroid treatment ($p = 0.02$), and reduced need of colectomy ($p = 0.02$) [10]. In a study by Schnitzler and co-workers, mucosal healing in CD was associated with decreased rate of major abdominal surgery (14.1% vs. 38.4%; $p < 0.0001$) and need for hospitalization compared to the patients who did not achieve mucosal healing (42.2% vs. 59.3%; $p = 0.0018$) [11].

Similarly, in patients with UC, a study by Ardizzone et al. showed that patients achieving complete endoscopic response (Baron score of 0) had lower rates of hospitalization (25% vs. 49%; $p = < 0.01$), lesser need of immunosuppressive therapy (5% vs. 26%; $p = < 0.003$), and lower rates of colectomy (3% vs. 18%; $p = 0.02$) compared to the patients with partial response (Baron score 1–3) [12]. Post-hoc analysis of active ulcerative colitis trial (ACT) showed that infliximab-treated patients with UC having lower Mayo endoscopic subscore at

Table 2 Most commonly used endoscopic indices in inflammatory bowel disease [2, 3]

Index	Proposed cutoffs for mucosal healing	Comments
Crohn's disease		
Crohn's Disease Endoscopic Index of Severity (CDEIS)	0–2	Detailed assessment, difficult to calculate in routine practice, partially validated, poor agreement for ulcers
Simple Endoscopic Score for Crohn's Disease (SES-CD)	0–2	Simplified version of CDEIS, partially validated, easy for clinical use, high degree of correlation with CDEIS for grading and responsiveness to changes
Ulcerative colitis		
Mayo score	0–1	Most commonly used, easy for clinical use, not validated
Ulcerative Colitis Endoscopic Index of Severity (UCEIS)	0–1	New index, not widely used, partially validated

week 8 had lower rates of colectomy by week 54 ($p = 0.0004$) and were more likely to have steroid-free clinical remission at week 54 ($p < 0.0001$) [13].

Risk of colorectal carcinoma

Persistence of mucosal inflammation can predict long-term development of colorectal carcinoma in IBD patients. Benefit of mucosal healing in reducing risk of colorectal carcinoma is predominantly shown in UC [14]. In a study by Rutter et al., multivariate analysis revealed that histologic inflammation score was the only risk factor for development of colorectal neoplasia in patients with long-standing, extensive UC ($p < 0.001$) [15]. Rutter et al. in their subsequent study showed that patients with macroscopically normal mucosa had 5-year cancer risk similar to that of the general population ($p = 0.003$), further emphasizing the importance of mucosal healing [16]. Recently, one meta-analysis have shown that patients with histological inflammation were at a higher risk of development of colorectal neoplasia compared to the patients with mucosal healing (OR = 2.6) [17].

Quality of life

Mucosal healing is associated with reduction in clinical activity as well as inflammation. Theede et al. studied 110 patients with UC. They found that poor health-related quality of life (HRQOL) index was associated with clinical disease activity and extent of involvement. In that study, patients with mucosal healing had better HRQOL index than those with active disease [18]. Casellas et al. studied 115 patients with IBD with mucosal healing (48 with CD and 67 with UC) for HRQOL index. In that study, they found that approximately 80% patients with mucosal healing had improvement in HRQOL index irrespective of the types of treatment [19].

Though the data are scanty, achievement of mucosal healing is also shown to be cost-effective as it reduces needs of hospitalization and surgery [20, 21] (Table 3).

Table 3 Benefits of mucosal healing in inflammatory bowel disease

- Better predictor of long-term clinical remission
- Prolonged steroid-free clinical remission
- Reduced need of hospitalization
- Reduced need of surgery
- Reduced penetrating complications in Crohn's disease
- Reduced risk of carcinoma in ulcerative colitis patients
- Better quality of life

Methods to assess mucosal healing

Endoscopic examination

Endoscopic examination by various scoring system is the most important tool to assess mucosal healing. It also helps in guiding management and increases the probability of achieving mucosal healing. Recently, a retrospective study has been conducted on 67 CD patients with the presence of ulcer on initial endoscopic examination. Follow up data were collected to see the achievement of mucosal healing at 52 weeks. They showed that the factors associated with achievement of mucosal healing were the time duration of < 26 weeks between consecutive endoscopic examination irrespective of clinical symptoms (hazard ratio [HR] 2.35) and adjustment of treatment when mucosal healing was not achieved (HR 4.28) [22]. A randomized multicentric controlled trial in CD patients (REACT II, an ongoing trial with enhanced algorithm), in which treatment is intensified as per endoscopic assessment, may be able to give more clarity regarding timing and frequency of repeated endoscopic examination to achieve mucosal healing and to reduce disease-related morbidity [23]. Similar study performed in UC patients also showed that repeated endoscopic examination is feasible and adjustment of treatment according to the endoscopic finding is associated with higher probability of achieving mucosal healing [24].

Role of newer techniques in endoscopy like chromoendoscopy and virtual chromoendoscopy (narrow band imaging [NBI] and I-Scan) have been also evaluated for better detection of inflammation. Though role of chromoendoscopy has been well-documented for detection of dysplasia, its role in detection of inflammation is still not known. A few studies showed the role of NBI for better detection of angiogenesis in patients with IBD [25, 26]. In one randomized control trial, virtual chromoendoscopy significantly improved diagnosis of severity and extent of the diease in patients with IBD compared to white light endoscopy [27]. Recently, one study has shown good correlation between magnified NBI findings and histological activity [28]. These studies show an upcoming role of image-enhanced endoscopy for better detection of inflammation in IBD patients.

Imaging

A subset of patients of CD has only small bowel involvement in whom documentation of mucosal healing is a challenging task. Moreover, as CD is a transmural disease, documentation of inflammation beyond mucosa is possible only with cross-sectional imaging. Cross-sectional imaging like computed tomography enterography (CTE), magnetic resonance enterography (MRE), or intestinal ultrasound can be useful for assessment of disease activity while on treatment. As

MRE is non-invasive, not associated with radiation exposure, and has ability to diagnose extraintestinal disease, it is one of the most commonly used cross-sectional imaging options for follow up of CD patients. Though initial studies showed inconsistent results, in a recent study by Ordas et al., 48 patients of CD with CDEIS score ≥ 7 and ulcers in ≥ 1 intestinal segment undergoing MRE and ileocolonoscopy at baseline and 12 weeks after treatment with corticosteroids or biological therapy showed encouraging results. Magnetic resonance index of activity (MaRIA) score was used in MRE for baseline and follow up evaluation. Half of patients achieved mucosal healing (CDEIS < 3.5) at week 12, and results of MaRIA and CDEIS was highly concordant ($r = 0.81$; $p < 0.001$). However, specificity for ulcer healing was low (69%), necessitating endoscopy for documentation of the same [29]. Recently, some studies also assessed role of serial MRE and small intestinal contrast ultrasound (SICUS) for follow up of CD patients on treatment to detect transmural inflammation as discussed at the end of this review article. However, role of imaging in UC is very limited [30].

Video capsule endoscopy

Video capsule endoscopy (VCE) is an important tool for diagnosis of small bowel lesions in patients with CD. A few studies have shown role of VCE in follow up of CD patients after treatment to document mucosal healing. In a recent study, patients with small bowel CD ($n = 43$) were followed with VCE using Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) at baseline, week 12, and week 52. At 52 weeks, 42% of patients had complete normalization of CECDAI index along with clinical and biochemical response. This study suggested potential role of VCE for follow up of CD patients with predominantly small bowel involvement to document mucosal healing [31, 32]. However, VCE for mucosal healing in patients with CD with predominantly colonic involvement in UC patients is not so promising and has poor sensitivity and specificity [33]. So, use of VCE to document mucosal healing should be restricted to CD patients with predominantly small bowel involvement [33]. Another limitation with use of VCE is high capsule retention rate up to 13% in patients with diagnosed CD, requiring strict patient selection [34].

Serum and fecal biomarkers

Various serum biomarkers like C-reactive protein (CRP), IL-6, erythrocyte sedimentation rate (ESR), fecal calprotectin (FC), fecal lactoferritin, fecal S100A12, M2-pyruvate kinase (M2-PK), serum amyloid A, human trefoil factor 3 etc. have been evaluated as non-invasive markers to predict mucosal healing in IBD patients [35, 36]. CRP is the most commonly used serum marker to document activity in patients with IBD. However, it correlated with disease activity better in CD patients than in UC patients [37]. CRP is useful for prediction of endoscopic disease activity, disease relapse, and response to therapy especially with various biological agents. CRP has also been shown to moderately correlate with endoscopic disease activity in some studies [37]. Mosli et al. conducted systemic review and meta-analysis for use of CRP, FC, and serum lactoferrin for detection of endoscopic disease activity in symptomatic IBD patients. They found that CRP had pooled sensitivity and specificity of 49% and 92% for prediction of endoscopic disease activity [38]. In one study involving 718 CD patients, high CRP levels were associated with higher response to infliximab therapy than normal levels ($p = 0.014$) and early normalization of CRP was associated with sustained long-term response ($p < 0.001$) and mucosal healing ($p = 0.033$) [39]. Another study also showed normalization of CRP at 12 weeks was associated with medium-term clinical efficacy and mucosal healing with adalimumab treatment in patients with CD [40].

FC has also been studied for its role to predict disease activity and mucosal healing in IBD patients on treatment. Similar to CRP, FC has been shown to have moderate to strong correlation with endoscopic disease activity in both UC as well as CD [37]. FC levels < 250 μg/g has been shown to predict mucosal healing with high accuracy, and level < 200 μg/g can predict histological remission with sensitivity and specificity of 71% and 76%, respectively [41, 42]. In a meta-analysis, FC had pooled sensitivity and specificity of 92% and 88%, respectively for predicting endoscopic disease activity [38] (Table 4).

Drugs useful for achieving of mucosal healing

Crohn's disease

Steroids and immunomodulators

Steroids have hardly been used for achieving mucosal healing in CD. Azathioprine (AZA) had better results compared to steroids. Rate of mucosal healing with azathioprine have been 40% to 50% in different trials [44, 45]. In a head-to-head comparison of AZA and budesonide for patients with steroid-dependent CD, AZA achieved higher rate of mucosal healing than budesonide (83% vs. 24%; $p < 0.0001$) [43]. Methotrexate (MTX) has also been used rarely to achieve mucosal healing in patients with CD. Laharie et al. compared MTX (15–25 mg/week), AZA (2–3 mg/kg), and infliximab (IFX) (5 mg/kg) in 41 CD patients. Mucosal healing was achieved in 11% of MTX compared to 50% of AZA-treated patients ($p = 0.011$ vs. MTX) and 60% of IFX-treated patients ($p = 0.008$ vs. MTX) [44].

Table 4 Various modalities for assessment of mucosal healing in patients with inflammatory bowel disease

Modality	Advantages	Disadvantages
Endoscopy	High sensitivity and specificity, most validated tool, histologic assessment possible, simultaneous therapeutic procedure possible (stricture dilatation)	Invasive, increases cost on repeated examination, gives no information regarding transmural inflammation
MRE	Non-invasive, small ± large bowel assessment possible, information regarding transmural inflammation available, and identification extraluminal complications possible	Limited availability, no histologic assessment possible, cost-effectiveness unclear, requires more validation before wide applicability
VCE	Non-invasive, primarily for small intestinal assessment, sensitivity is high	Modest specificity, retention and incomplete assessment are the limitations, no histologic assessment possible, under-estimates colonic disease, cost-effectiveness unclear
Serum and fecal biomarkers	Non-invasive, easy to use, good correlation with mucosal healing	Histological assessment not possible, requires more validation

MRE magnetic resonance enterography, *NPV* negative predictive value, *VCE* video capsule endoscopy

Biologicals

Several biological agents have been tried to achieve mucosal healing in CD patients. In SONIC trial, IFX and AZA were used either alone or in combination. Mucosal healing at week 26 was significantly higher with combination therapy (43.9%) compared to AZA alone (16.5%; $p < 0.001$) [45]. In a recent study, IFX trough levels were found to be better predictor of mucosal healing and clinical response than measurement of anti-infliximab antibody levels [46]. In EXTEND trial, patients were randomized to receive either adalimumab (ADA) treatment only for induction of remission followed by placebo or ADA for both induction and maintenance. ADA maintenance group had higher mucosal healing rates compared to placebo group at week 52 (24.2% vs. 0%; $p < 0.001$) [47]. In a multicenter trial of certolizumab (MUSIC study), 89 patients with active CD were treated for 52 weeks. Though endoscopic response at weeks 10 and 54 were 54% and 49%, respectively, rates of mucosal healing (CDEIS < 3) were only 4% and 8%, respectively [48].

Newer agents

Vedolizumab is an anti-α4ß7 integrin antibody approved for treatment of CD patients. Dulai et al. studied 212 patients with moderate–severe CD treated with vedolizumab. Mucosal healing and deep remission (mucosal healing with clinical remission) rates were 63% and 26% at week 52 [49]. One recent study has shown mucosal healing of 35% among 171 IBD patients on vedolizumab, and no relationship was found between vedolizumab trough levels and mucosal healing [50]. Ustekinumab is an anti-IL12/23 antibody recently approved for CD. In GETAID trial, 122 CD patients on ustekinumab therapy showed mucosal healing in 39% of patients at 26.6 months of follow up [51]. In study by Rutgeerts et al., patients on ustekinumab therapy tended having higher mucosal healing than placebo at week 44 (13.0% vs 4.2%) [52]. Tofacitinib (janus activated kinase [JAK] inhibitor, preferentially affecting JAK1 and JAK3), has shown promising results in UC patients but has failed to reproduce the same results in CD patients [53]. Filgotinib, an oral selective JAK1 inhibitor, was tested in 174 moderate–severe CD patients that showed mucosal healing only in 4% of patients at 10th week [54]. Risankizumab is a humanized monoclonal Ig G1 antibody targeting interleukin 23 plays a key role in regulation of various immune cells and inflammation. In a recently published trial, risankizumab was found to be more effective than placebo in inducing remission in moderate–severe CD patients ($p = 0.04$) [55]. In maintenance trial, it has shown higher mucosal healing rate compared to placebo at week 52 (33% vs. 21%) [56] (Table 5).

Ulcerative colitis

5-Aminosalicylic acid

Though 5-aminosalicylic acid (5-ASA) compounds have not been found to be useful for induction of mucosal healing in patients with CD, their role in UC has been established in a few studies. Post-hoc analysis of ASCEND I and II trials showed that at week 6, mucosal healing rate was higher with 4.8 g/day mesalamine compared to 2.4 g/day (80% vs. 68%; $p = 0.012$) [57]. In mild to moderate active UC, mesalamine 2 g/day orally and 2 g/day enema had better mucosal healing (71%) compared to oral mesalamine 4 g/day alone (58%) [58].

Steroid and immunomodulators

Steroids have been rarely used to achieve mucosal healing in patients with UC. In a study by Ardizzone et al., 157 patients

Table 5 Drugs used to achieve mucosal healing in Crohn's disease

Study	Drugs used	Definition of mucosal healing	Time of endoscopy	Mucosal healing (%)
Mantzaris et al. [43]	AZA 2–2.5 mg/kg/day vs. budesonide 6–9 mg/day	CDEIS < 4	Week 52	83% vs. 24%
Laharie et al. [44]	MTX 15–25 mg/week vs. AZA 2–3 mg/kg/day vs. IFX 5 mg/kg	CDEIS < 4		11% vs. 50% vs. 60%
Colombel et al. [45]	AZA 2.5 mg/kg/day vs. IFX 5 mg/kg vs. AZA 2.5 mg/kg + IFX 5 mg/kg	Absence of ulcer and/or erosion	Week 26	16% vs. 30% vs. 44%
Rutgeerts et al. [47]	ADA maintenance vs. placebo	CDEIS < 4	Week 52	24% vs. 0%
Dulai et al. [49]	Vedolizumab	Absence of ulcer and/or erosion	Week 52	63%
Wils et al. [51]	Ustekinumab	Absence of ulcer and/or erosion	Median follow up: 40 weeks	39%
Feagan et al. [56]	Risankizumab 200 mg vs. risankizumab 600 mg vs. placebo	CDEIS ≤ 4	Week 52	18% vs. 33% vs. 21%

AZA azathioprine, *IFX* infliximab, *MTX* methotrexate, *ADA* adalimumab, *CDEIS* Crohn's Disease Endoscopic Index of Severity

with UC were followed up for 12 months after their initial need for systemic corticosteroid treatment (40–60 mg of oral prednisolone/day or parenteral methylprednisolone). In their study, 38% of patients achieved mucosal healing at 3 months as assessed by modified Baron score [12]. In a recent study by Van Assche et al., 282 patients with UC were randomized to receive either beclomethasone dipropionate (BDP) or oral prednisolone; both the arms showed similar rates of mucosal healing at week 4 (23% vs. 19%; $p = 0.38$) [59]. Ardizzone et al. compared AZA (2 mg/kg/day) with mesalamine (3.2g/day) on 72 patients with steroid-dependent UC. Clinical and endoscopic steroid-free remission was found more with AZA therapy compared to mesalamine (53% vs. 19%; $p = 0.006$) [60]. Data regarding efficacy of calcineurin inhibitor in achieving mucosal healing are scarce. However, tacrolimus has also been shown to be effective in inducing mucosal healing in UC. In a recent randomized trial, oral tacrolimus was associated with higher mucosal healing rates compared to placebo (43.8% vs. 13.3%; $p = 0.012$) [61].

Biologicals

In ACT1 and ACT2 trials, patients with active moderate to severe UC were randomized to receive IFX (5 mg/kg or 10 mg/kg) or matching placebo at weeks 0, 2, and 6 and then every 8 weeks. Mucosal healing occurred more commonly with both doses of IFX compared to placebo in both the trials at week 30 ($p < 0.001$) [62]. Similar to CD, combination therapy of IFX with AZA had higher mucosal healing rates compared to AZA alone (62.8% vs. 36.8%; $p = 0.001$) [63]. ULTRA studies have shown mucosal healing efficacy of ADA in UC. In ULTRA-2 trial, mucosal healing with ADA in patients without prior exposure of anti-TNF-α agents was higher than placebo at week 52 (31.3% vs. 19.3%; $p = 0.018$) [64]. In a recently published study, ADA achieved 50% mucosal healing and 17.6% of patients achieved histological remission [65]. In one recent network meta-analysis, ADA therapy was found inferior to IFX (OR 0.45) and combination IFX-AZA therapy (OR 0.32) for inducing mucosal healing. However, no difference was found between TNF-α inhibitors and vedolizumab for inducing remission [66]. Studies have shown that efficacy of golimumab is equivalent to infliximab in achieving mucosal healing [67]. In PURSUIT-SC trial, different doses of golimumab were compared with placebo. Mucosal healing rates were higher in patients on any dose schedule of golimumab compared to placebo ($p < 0.0014$, for all comparisons) [68]. Recently, one study showed 40% mucosal healing rate in 91 patients with moderate to severe UC on golimumab therapy. They showed that achievement of short-term mucosal healing at 14 weeks was associated with intervention-free survival and discontinuation-free survival at week 52 [69].

Newer agents

Vedolizumab, α4β7 antagonist, showed better mucosal healing rates compared to placebo in GEMINI 1 study at both week 6 and week 52 ($p < 0.001$) [70]. One recent multicenter study found that early (at week 6) vedolizumab trough level (> 18 μg/mL) predicts mucosal healing at 1 year [71]. Tofacitinib is an oral, small molecule JAK inhibitor that preferentially inhibits JAK1 and JAK3. OCTAVE studies identified its role in induction as well as maintenance of UC. Tofacitinib had higher mucosal healing rate than placebo at week 8 ($p < 0.001$) as well as at week 52 (37.4% vs. 13.1%; $p < 0.001$) [72]. Peficitinib is JAK1, JAK2, and JAK3 inhibitor with six to seven times more affinity for JAK3 receptor. In a phase 2b dose-ranging trial, peficitinib has shown higher clinical response and mucosal healing rates compared to placebo [73]. The sphingosine-1-phosphate (S1P) subtype 1 (S1P1) receptor plays a crucial role in the trafficking of lymphocytes from lymphoid organs. Ozanimode, S1P1, and S1P5 receptor modulator decreases trafficking of lymphocytes from lymphoid organs. In a recently published trial, it showed better clinical response and mucosal healing rates compared to

placebo (34% vs. 12%; $p < 0.002$) [74]. Matrix metalloproteinase-9 (MMP-9) may contribute to pathogenesis of UC by causing destruction of basement membrane and alteration in intestinal mucosal integrity. Recently, anti-MMP-9 (andecaliximab) antibody has been tried in moderate to severe UC without promising results [75]. Though ustekinumab therapy has shown promising results in CD, its efficacy in UC is limited to small studies only [76]. However, larger studies are going on to evalaute its efficacy in UC [77] (Table 6).

New approaches for targeting mucosal healing

Target-to-treat approach

As described above, due to the presence of large discrepancy between clinical symptoms, biomarkers, and endoscopic disease activity, Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) consensus described treatment goals in IBD [30]. In that statement, they had identified composite end point of therapy as clinical/patient-reported outcome (PRO) remission (for CD: resolution of abdominal pain and diarrhea/altered bowel habits; for UC: resolution of rectal bleeding and diarrhea/altered bowel habits) and endoscopic remission (mucosal healing). Patients should be assessed at minimum of 3 months for clinical/PRO remission during active phase, and endoscopy should be performed at 3–6-month interval for endoscopic remission during active phase. They stated that imaging should be used in CD to evaluate the inflammation when endoscopic assessment is not possible. Histological remission was not defined as a target for therapy either in UC or CD due to lack of sufficient evidence. Biomarkers (CRP and fecal calprotectin) can be used as adjunctive to clinical and endoscopic assessment. However, treatment decision based only on biomarkers was not advised [30]. Mucosal healing as discussed above is one of the important targets in "target-to-treat" approach. Various clinical studies as described above that used clinical remission and mucosal healing as a primary end point of therapy proved that these targets are feasible to achieve and are associated with better steroid-free clinical remission and decreased disease-related morbidity without significantly increased risk of drug-related side effects [55, 70, 72].

Early combined immunosuppression approach

Recently, a few studies have shown usefulness of top-down strategies in management of IBD especially in CD. Due to progressive disease behavior, especially in CD, there appears to have a window period in which combination therapy or early aggressive therapy can be beneficial in changing natural history of the disease as well as in reducing disease-related morbidity and mortality. In CD, patients aged < 40 years, perianal and stricturing disease, initial requirement of steroid, and loss of > 5 kg weight have been identified as being severe or "disabling" disease [78, 79]. Use of immunosuppressant or biological therapy early in course of disease (< 2 years) might be beneficial to reduce long-term morbidity. D'Haens et al. had done multicentric open-label study on 133 newly-diagnosed CD patients and randomly assigned them either to early combined immunosuppression (ECI) or conventional therapy. In ECI group, patients received induction doses of INX along with AZA, while in conventional group, patients received steroid, followed in sequence by AZA and IFX, if needed. Patients in ECI group had higher steroid-free clinical remission at week 52 (61.5% vs. 42.2%; $p = 0.02$) without increasing risk of adverse events [80]. Recently, another large multicentric trial (REACT) also evaluated the role of ECI vs. conventional therapy. In that study, though steroid-free clinical remission at week 52 did not differ between the two groups, composite index of major disease-related events like hospitalization, need for surgery, or major

Table 6 Drugs used to achieve mucosal healing in ulcerative colitis

Study	Drug used	Definition of mucosal healing	Time of endoscopy	Mucosal healing (%)
Lichtenstein et al. [57]	Mesalamine 4 8 g/day vs. 2.4 g/day	Mayo score 0 or 1	Week 6	80% vs. 68%
Ardizzone et al. [12]	Prednisolone 40–60 mg/day	Modified Baron score = 0		38%
Van Assche et al. [59]	Baclomethasone dipropionate 5 mg/day vs. prednisolone 40 mg/day	Disease Activity Index = 0	Week 4	19% vs. 23%
Ardizzone et al. [60]	AZA 2 mg/kg/day vs. mesalamine 3.2 g/day	Baron score 0 or 1	Week 24	53% vs. 19%
Rutgeerts et al. [62]	IFX 5 mg/kg vs. IFX 10 mg/kg vs. placebo	Mayo score 0 or 1	Week 52	18% vs. 45% vs. 47%
Sandborn et al. [64]	ADA vs. placebo	Mayo score 0 or 1	Week 52	25% vs. 15%
Feagan et al. [70]	Vedolizumab every 8 weeks vs. every 4 weeks vs. placebo	Mayo score 0 or 1	Week 52	52% vs. 56% vs. 20%
Sandborn et al. [72]	Tofacitinib 5 mg vs. 10 mg groups vs. placebo	Mayo score 0 or 1	Week 52	37% vs. 45% vs. 13%
Sandborn et al. [74]	Ozanimod 0.5 mg vs. 1 mg vs. placebo	Mayo score 0 or 1	Week 8	28% vs. 34% vs. 12%

AZA azathioprine, *IFX* infliximab, *ADA* adalimumab

disease-related side effects occurred less frequently in ECI group ($p = 0.003$) [81].

Tight control approach

In treat-to-target approach, the main goal of therapy was clinical and endoscopic remission. The panel advised that biomarkers (CRP and FC) should be used as adjunctive measure to detect inflammation in monitoring of patients with CD. However, treatment adjustment should not be done based only on elevation of these markers, and endoscopy should be performed before any treatment escalation [30]. However, in routine clinical practice, repeated endoscopic evaluation for treatment adjustment is invasive, costly, and often, not feasible. So, recently, a large multicentric trial (CALM trial) has evaluated role of biomarkers (CRP and FC) in treatment adjustment. They randomly assigned 244 patients with CD in either tight control (TC) group or conventional management group. In TC group, decision regarding treatment escalation was made based on biomarkers and clinical disease activity (FC ≥ 250 μg/g, CRP ≥ 5 mg/L, CDAI ≥ 150, or use of steroid in last week were used as failure criteria). While in conventional management group, treatment escalation was made based on clinical symptom-based score (CDAI ≥ 200, CDAI fall < 100 compared to baseline, or use of steroid in last week). In both the groups, patients meeting failure criteria at prespecified clinical visit underwent treatment escalation from steroid to ADA on alternate week, ADA every week, and lastly, both weekly ADA and daily AZA, sequentially. At week 48, patients in TC group achieved significantly higher rate of mucosal healing than patients in the conventional group (46% vs. 30%; $p = 0.01$). Risk of adverse events was similar in both the groups. They concluded that treatment escalation based on both clinical score and biomarker resulted in better outcome compared to only clinical symptom-based decisions [82].

Though these treatment approaches like ECI or TC have shown better clinical outcome such as clinical and endoscopic remission than conventional management, whether such aggressive approach is associated with change in natural history of disease or not remains to be proved. Moreover, as usual follow up of these trials is 12–24 months, long-term consequences or side effects of these approaches remains to be answered. So, at this point, this approach (ECI or TC) remains mainly in realm of clinical trials rather than routine clinical practice.

Targets beyond mucosal remission

Histological remission

In the recent years, histological remission has emerged as an additional target with an idea of healing beyond the macroscopic appearance. Though not clearly defined, IOIBD has proposed absence of neutrophils in crypts and lamina propria, absence of basal plasma cells, and reduced lamina propria eosinophils to normal as a definition of histological remission in IBD [9]. Being a discontinuous and transmural disease, histological remission is less clearly defined in CD compared to UC with the presence of poorly defined and non-validated scoring systems. So, histological healing is mainly important for UC as it will define the complete remission and may be associated with better clinical outcome compared to mucosal and clinical remission [9]. A few recent studies in UC have shown that endoscopically normal mucosa might still have histological inflammation, which may increase the risk of disease relapse. Recently, Ozaki et al. have studied 194 patients of UC with mucosal healing (Mayo endoscopic score ≤ 1) and evaluated them for a median period of 20 months. During the study period, 34.5% patients had clinical relapse; the presence of crypt architectural abnormality and mucin depletion on histology were associated with increased risk of relapse [83]. Similarly, in a study by Azad et al., increased eosinophils and neutrophils in lamina propria were associated with a high rate of relapse [84]. Narang et al. evaluated 46 UC patients with mucosal healing. They showed that patients with histological remission had lower relapse rate at 1 year compared to patients with histologically active disease (12.9% vs. 53.3%) [85]. Histological activity is also associated with increased risk of development of dysplasia. In a study by Rutter et al., only histological activity was associated with increased risk of development of dysplasia on multivariate analysis [15]. Similarly, one recent retrospective study also showed that mean severity of microscopic inflammation during the surveillance period (over 5–10 years) is an accurate marker of risk of colorectal neoplasia [86]. Moreover, studies have shown poor correlation between endoscopic and histological remission necessitating detailed histological examination even in patients with endoscopic remission [87].

The presence of various histological scores, heterogenicity in definition of histological remission, and lack of robust evidence are the primary hindrances in making histological remission as a target of therapy [30]. Geboes score is one of the most widely used scores and a cut-off value of ≤ 3.0 is considered as histological remission; however, it is not validated and kappa values between observers were also very low [88]. Moreover, its correlation with Mayo endoscopic subscore is only moderate ($r = 0.482$) [89]. Recently, two new validated histological scores have been developed in UC. Nancy index (NI) is based on five-grading system (grades 0–4) using three parameters: acute inflammatory cell infiltrate, chronic inflammatory cell infiltrate, and ulceration [90]. Nancy grade 0 or 1 represents histological remission [90]. Roberts histological index (RHI) is also recently developed and validated histological score for UC. It involves four histological parameters: epithelial, and lamina propria neutrophils, chronic

inflammatory cell infiltrate, and erosion or ulceration. RHI score varies from 0 to 33 with score ≤ 3 indicative of histological remission [91]. Recently, one study has shown good correlation between UCEIS and histological indices (NI [r = 0.84] and RHI [r = 0.86]) [92]. Better validated and uniform histological scores are needed for uniform definition of histological remission.

Transmural or mucosal healing in CD

CD is a transmural disease unlike UC, which is only a mucosal disease. Whether only mucosal healing represents complete transmural healing or not is still a matter of debate. Cross-sectional imaging is useful to judge transmural inflammation in CD patients. Studies have used various imaging modalities like MRE, CTE, or SICUS to judge intestinal inflammation in CD. MRE is helpful in judging severity of disease by wall thickening, intramural edema, or hypo-intensity on T2-weighted imaging and increased intramural signal on diffusion-weighted images apart from judging the length of intestinal involvement [93]. In MRE, most commonly used score is MaRIA, which is a composite index of contrast enhancement, wall thickening, edema, and ulceration in each segment. In SICUS, bowel wall thickness is measured to identify degree of inflammation; however, any validated composite index is not available [94]. In a study by Castiglione et al., 80 patients with CD were evaluated by colonoscopy, MRE, and IUS. Only a quarter of patients had achieved transmural healing in that study. Transmural healing by both modalities had good correlation, but transmural healing had poor correlation with clinical remission [95]. Civitelli et al. studied 32 patients with CD with SICUS at baseline and at 9 to 12 months after therapy. They defined transmural healing as bowel wall thickness of < 3 mm along with normalization of all SICUS parameters on follow up. In their study, 38% patients had mucosal healing, 12.5% had transmural inflammation, and 66% with mucosal healing had persistent transmural inflammation [96]. Fernandes et al. studied 214 patients with MRE and colonoscopy every 6 months and defined transmural healing as mucosal healing with inactive MRE. In their study, transmural healing was associated with lower rates of hospital admission, therapy escalation, and surgery than mucosal healing only [97]. These studies suggest that in patients with CD, complete healing is much more complex than just mucosal healing. However, ideal modality to diagnose transmural healing and its sequential use to guide modification of therapy remains to be answered.

Future research

Even though with recent therapy mucosal healing is an achievable target, how to maintain the mucosal healing is still a question to be answered. All recent trials on mucosal healing have targeted clinical, biochemical, or endoscopic criteria for escalation therapy to achieve mucosal healing, but on achieving mucosal healing, how to de-escalate therapy is still not known. Whether histological and/or transmural healing adds further advantage over mucosal healing or not and their feasibility in clinical practice requires further exploration.

Compliance with ethical standards

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Conflict of interest JS, MLT, and UD declare that they have no conflict of interest.

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